ANNALS OF
INTERNAL MEDICINE

VOLUME 43 AUGUST, 1955 NUMBER 2

AN EVALUATION OF THE SERUM IRON IN LIVER DISEASE *

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THE internal redistribution of iron in the body occurs through the serum iron compartment, with the liver playing an important rôle. Yet determinations of serum iron levels in liver diseases were few in the English literature until 1949. The foreign journals, however, contained observations of serum iron changes in liver diseases, which were first reported in 1927 by Warburg and Krebs.[1] This foreign literature was recently reviewed by Ducci, Spoerer and Katz,[2] who found that most foreign investigators considered the serum iron levels of value in the differential diagnosis of jaundice.

In this country Moore, Doan and Arrowsmith[3] in 1937, during their study of iron transportation and metabolism, recorded serum iron levels in three patients, one patient each with acute yellow atrophy, portal cirrhosis and hemochromatosis. Rath and Finch[4] in 1949 reported serum iron levels in nine patients with liver disease which included hepatitis and cirrhosis of the liver. In the same year Howard,[5] stimulated by finding high serum iron levels in two cases of hemochromatosis, studied 31 patients with various types of parenchymal liver disease.

During 1952 Matassarin and Delp,[6] Peterson[7] and Ducci, Spoerer and Katz[2] each contributed a report of serum iron in liver disease. These three papers represented serum iron levels in 284 patients. Finally, two years later, Christian[8] studied serum iron levels in 193 persons with various types of liver diseases. Table 1 is a summary of the serum iron levels in the usual liver diseases reported in the papers cited above.

The purpose of this paper is to report the serum iron levels in 61 patients with liver disease. It is well known and adequately shown by Weisbrod and Schiff[12] that by using a battery of liver function tests alone the diagnosis of viral hepatitis is only 67% accurate, and in obstructive jaundice only 41%

* Received for publication December 15, 1954.
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accurate. It seems fruitless to add another test to this battery unless it can be shown that its use is superior to one or more of those tests commonly employed at present, and that the test is simple enough to be performed in the average well equipped laboratory.

Material

The 61 patients studied were admitted to the Veterans Administration Hospital in Coral Gables, Florida. There were 60 males and one female. The ages varied from 21 to 78 years. Twenty-five healthy male employees were selected to determine the normal range in this laboratory of the serum iron in the age group of 21 to 63 years. The diagnosis of the 61 patients was made by history, physical examination and laboratory studies. The

Table 1

Serum Iron Levels in Liver Diseases as Reported in the American Literature

Investigator	Acute Hepatitis		Portal Cirrhosis		Obstructive Jaundice		Normal Values		
	No. Cases	Mean Gamma %	No. Cases	Mean Gamma %	No. Cases	Mean Gamma %	No. Controls	Mean Gamma %	Range Gamma %
*Rath and Finch[4] (1949)	1	121	8	110	—	—	30	100	72–147
*Howard[5] (1949)	5	179	12	87	—	—	28	121	65–216
*Matassarin and Delp[6] (1952)	7	268	4	89	8	140	35	80(M) 77(F)	40–145
Peterson[7] (1952)	60	295	15	110	10	155	50	130	—
*Ducci, Spoerer and Katz[2] (1952)	62	237	68	97	—	—	40	108.4	62–168
Christian[8] (1954)	33	297	23	139	14	137	50	143	70–286
Authors (1954)	17	240	34	102	10	115	25	108.4	70–170

* Mean values were calculated from investigators' tables.

diagnosis was confirmed by liver biopsy in 56 patients, and at operation or at the postmortem table on the other four patients. A total of 147 serum iron determinations was made on these 61 patients.

Methods

Serum iron determinations were done by a modification of the method described by Barkin and Walker [9] on morning fasting blood drawn without hemolysis with iron-free needles and syringes. The blood was allowed to clot in iron-free tubes and the serum removed within one hour. Ascorbic acid was used as a reducing agent, and *o*-phenanthroline was used for the color complex. The transmittancy of the sample was read at a wave length of 520 μ on the Leitz photrometer.

The liver function tests, including serum bilirubin, cholesterol, cholesterol esters, alkaline phosphatase, cephalin flocculation, thymol turbidity and Bromsulphalein extraction, were all done by the standard methods. In addition, total proteins, albumin, globulin and prothrombin time were done at least once on each patient. The criteria used in histologic diagnosis of the needle biopsy material were similar to those described by Smetana, Keller and Dubin.[10]

The serum iron level in 25 normal subjects between the ages of 21 to 63 years ranged from 70 to 170 gamma %, with a mean of 108.4 gamma %. This mean correlated well with the mean of 100 gamma % by Rath and Finch,[4] and the mean of 108.4 determined by Ducci et al.[2]

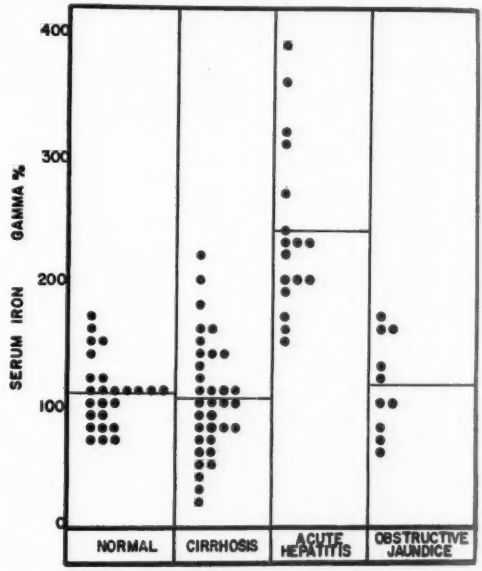

FIG. 1. Scattergram of the over-all results found in 25 healthy subjects and 61 patients with liver disease.

RESULTS

The 61 patients in this study included 17 patients with acute viral hepatitis, 34 patients with portal cirrhosis, and 10 patients with obstructive jaundice. The over-all results are seen in the scattergram of figure 1.

Cirrhosis of the Liver: Thirty-four patients with portal cirrhosis had a mean serum iron level of 102 gamma %. Their ages were between 29 and 63 years, with an average age of 50 years. Three patients showing predominantly fatty metamorphosis by liver biopsy had serum iron levels of

TABLE 2

Portal Cirrhosis—34 Cases

No. Cases	Jaundice	Ascites	Range Serum Iron Gamma %	Mean Serum Iron Gamma %	Mean Hemoglobin Gm./100 ml.
15	0	0	50–220	109	13.0
5	0	+	50–150	100	12.0
8	+	0	75–200	119	12.4
4	+	+	80–110	98	11.1
2*	0	0	20–35	27.5	7.5

* Gastrointestinal bleeding.

60, 50 and 200 gamma %. The patient with the iron level of 200 gamma %, an alcoholic, had a bilirubin of 22 mg. %, and his liver was tender and enlarged 6 cm. below the subcostal margin. The liver biopsy revealed advanced fatty metamorphosis with no fibrosis.

The other 31 patients showed the typical picture of portal cirrhosis in various degrees of severity. The patient with the highest serum iron of

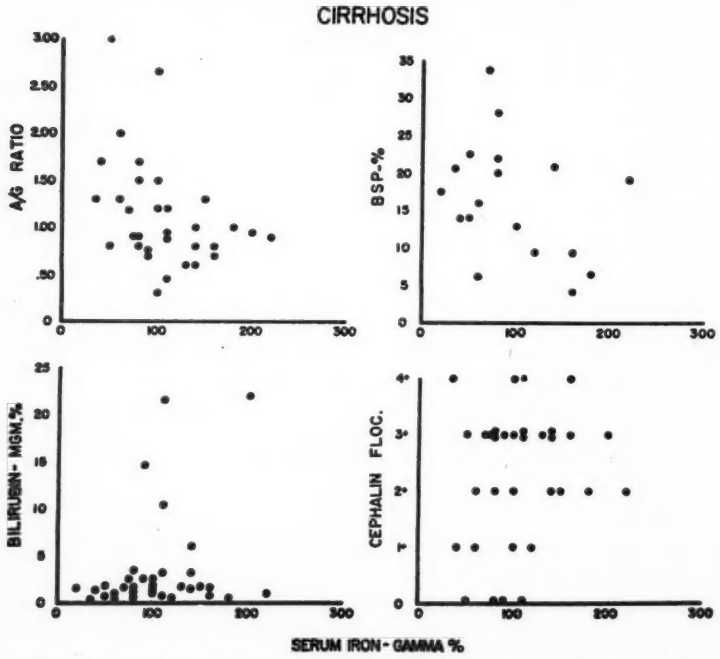

FIG. 2. Serum iron levels in cirrhosis expressed in gamma per cent plotted against the A/G ratio, Bromsulphalein extraction at the end of 45 minutes, serum bilirubin in milligrams per cent and cephalin flocculation in Hanger units.

220 gamma % was non-icteric, with a reversal of the A/G ratio and a large liver extending 8 cm. below the subcostal margin. Of the 34 cirrhotics, five had abdominal ascites, eight were jaundiced and four had both ascites and jaundice. Two had massive gastrointestinal hemorrhage due to esophageal varices.

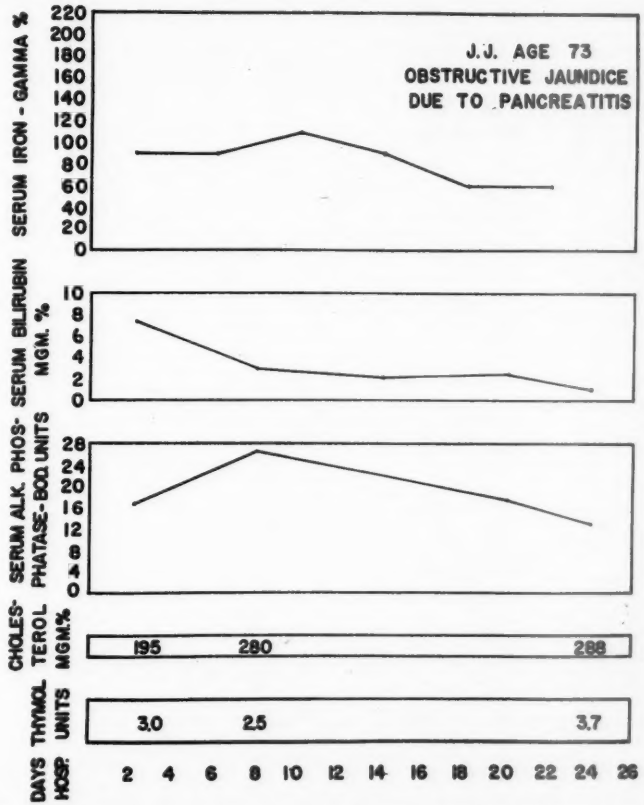

FIG. 3*A*. Serial serum iron levels, serum bilirubin, alkaline phosphatase, total cholesterol and thymol turbidity in a patient with obstructive jaundice due to chronic pancreatitis, showing the relatively flat curve of serum iron during period of recovery from obstruction of the biliary passages.

As seen in table 2, there was no significant difference of serum iron levels in the cirrhotic patients that could be ascribed to jaundice when present. The average serum iron difference between these patients varied only 20 gamma %. However, in cirrhotic patients with bleeding when the hemoglobin was below normal, the serum iron was also low. The two patients

with a serum iron level average of 27.5 gamma % in this group had evidence of gastrointestinal bleeding. As seen in figure 2, there was no correlation between the serum iron level and any of the so-called liver function tests.

Obstructive Jaundice: Ten patients with obstructive jaundice between the ages of 44 and 78 years of age were studied. The obstruction was

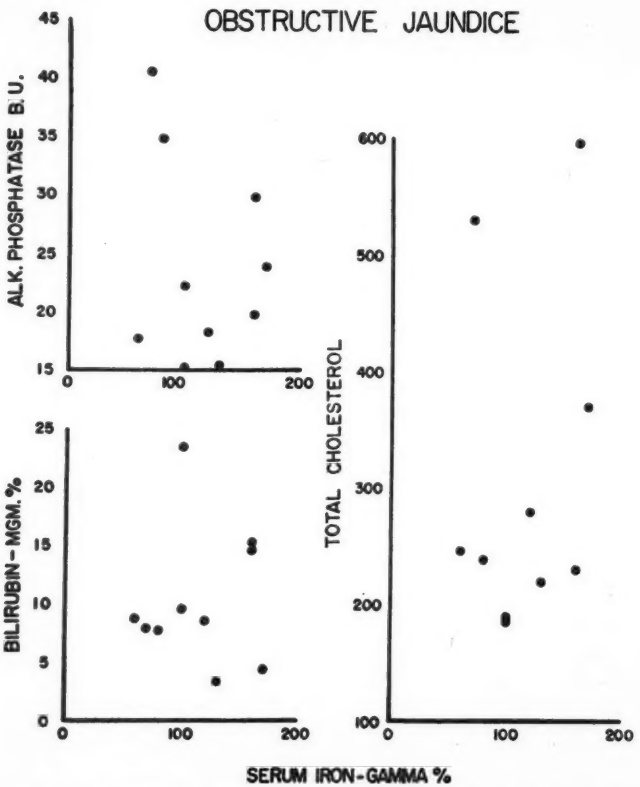

FIG. 3*B*. The serum iron levels in obstructive jaundice plotted against alkaline phosphatase in Bodansky units, bilirubin in milligrams per cent and total cholesterol.

caused by carcinoma in six patients and by common duct stone in three patients; it was unexplained in the one remaining patient in spite of exploratory laparotomy. Liver biopsy in all patients revealed the typical findings of obstructive jaundice. Four of the patients with carcinoma have since died, and the diagnosis of obstructive jaundice due to carcinoma has

been reconfirmed. The serum iron in this group of patients varied from a low of 60 gamma % to a high of 170 gamma %, with an average of 116 gamma %. When serial determinations are carried out on patients with obstructive jaundice the serum iron usually remains fairly constant until surgery, when it drops due to blood loss. Serial determinations done on one patient not included in this reported series is shown in figure 3A.

There was no apparent correlation, as is shown in figure 3B, between serum iron and alkaline phosphatase, bilirubin and total cholesterol.

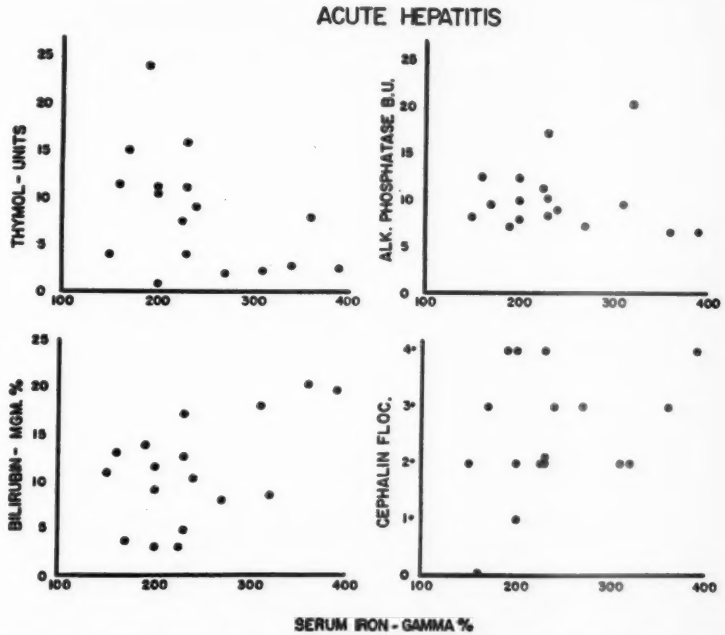

FIG. 4. Serum iron levels in acute hepatitis plotted against thymol turbidity in Maclagan units, alkaline phosphatase in Bodansky units, serum bilirubin in milligrams per cent and cephalin flocculation in Hanger units.

Acute Hepatitis: In this third group of patients studied, which included 17 patients with acute hepatitis, a serum iron range of 150 to 390 gamma % was found, with a mean of 240 gamma %. These determinations included the highest serum iron value in individual patients. As seen in table 1, the mean reported by other investigators varied from 121 to 297 gamma %.

No correlation was found between the serum iron and any of the liver function tests, as is shown in figure 4.

If serum iron levels are determined frequently on the same patient with

acute hepatitis, there is a period when the levels become progressively higher, followed by a period of declining levels.

Two cases of acute hepatitis are described below to demonstrate the changes in the serum iron curve in relation to the patient's clinical course.

Case Reports

Case 1. A 29 year old white male was considered to be a moderately severe case of acute hepatitis. He entered the hospital with a history of jaundice for seven days prior to admission. The liver was enlarged two fingerbreadths below the sub-

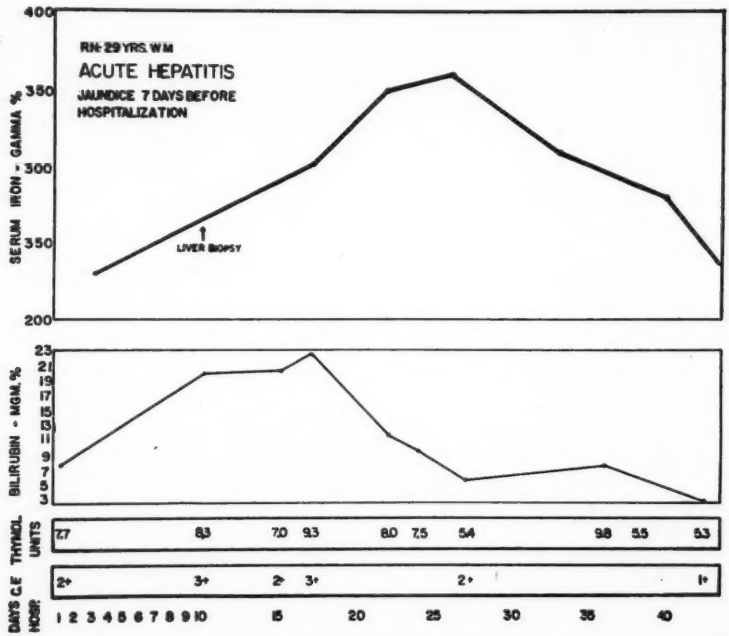

Fig. 5. Serial serum iron levels, bilirubin, thymol turbidity and cephalin flocculation in a patient with a prolonged course of acute hepatitis, showing the gradual rise and slow fall in serum iron levels.

costal margin, with tenderness on palpation. This patient's laboratory values and serum iron curve are seen in figure 5. The serum iron levels were 230, 300, 350, 360, 310, 280 and 190 gamma %. These levels were determined over a period of 52 days. The highest serum iron level occurred 31 days after the onset of jaundice. A liver biopsy performed 17 days after the onset of jaundice revealed large areas of focal necrosis of the parenchymal cells, many inflammatory cells in the sinusoidal areas, and numerous large Kupffer's cells containing lipochromic pigment and Councilman bodies.

The serum iron level was still rising in the presence of a falling serum bilirubin.

During hospitalization there was a drop in the hemoglobin level from 13.25 gm. to 10.72 gm., with a decline in the hematocrit from 46% to 35%.

The serum iron curve shows a slow rise and a slow fall in the serial iron determinations.

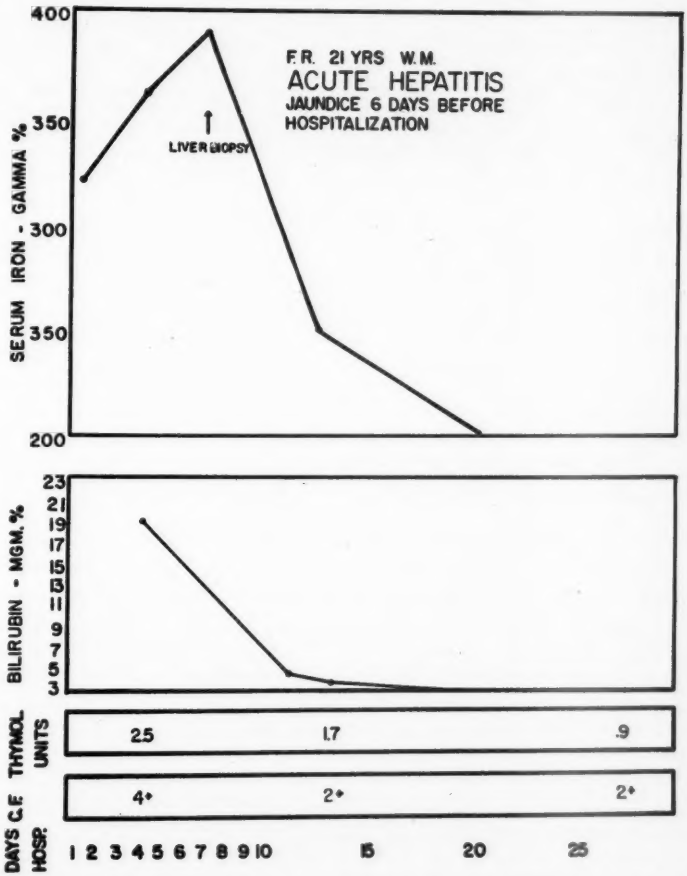

FIG. 6. Serial serum iron levels, serum bilirubin, thymol turbidity and cephalin flocculation in a patient with mild acute hepatitis, showing the rapid rise and rapid fall in serum iron level in a patient with a short, uncomplicated clinical course.

This patient returned to the hospital nine months after discharge with complaints of weakness, fatigue and right upper quadrant tenderness. The liver edge was palpable 3 cm. below the costal margin in the midclavicular line and was tender to percussion. All liver function tests were normal. The serum iron was 195 gamma % and the liver biopsy was considered normal.

Case 2. A 21 year old white male clerk entered the hospital with a history of jaundice for six days prior to admission. The liver was barely palpable but not tender. This patient was considered clinically to be a mild case of acute hepatitis. His laboratory determinations are presented in figure 6. The serial serum iron determinations were 320, 360, 390, 250, 120 gamma %. The highest value was found 12 days after the onset of jaundice. The serum iron had reached a normal level 36 days after the onset of jaundice.

The liver biopsy revealed moderate cellular infiltration in the sinusoidal areas, scattered areas of focal necrosis of the hepatic parenchymal cells and very little hepatic cellular degeneration, with a very occasional Councilman body. This biopsy was interpreted as one of mild hepatitis. It is seen that the serum iron curve has a fairly rapid rise and then a sudden drop within a period of five days. This patient's hospital course was uneventful.

Discussion

In cirrhosis of the liver the serum iron level was found within the normal range in the majority of patients. The extremely low serum iron levels found in this disease would be consistent with the presence of gastrointestinal bleeding. Other investigators have suggested that high serum iron levels in this disease represent parenchymal cell necrosis. This was not the experience in the study of the group of patients reported here. The presence or absence of jaundice or ascites had little effect on serum iron levels.

The cause for the elevation of the serum iron in hepatitis is as yet unknown. The iron may be released during liver cell destruction; however, the inability of a damaged liver to store iron may also be a factor.

Two patients not reported in this series were diagnosed as cirrhotics until elevated serum irons of 195 gamma % were found. Liver biopsy in these two instances revealed hemosiderosis. It is known that high serum iron levels are a common finding in patients with hemochromatosis and hemosiderosis.

The finding of an elevated serum iron in patients with hepatomegaly should make one consider the more unusual diseases.

In patients with obstructive jaundice, serum iron levels were within the normal range. The serial serum iron determinations are helpful in these patients in the differential diagnosis of acute viral hepatitis.

Acute hepatitis is characterized by elevated serum iron levels, which reach a peak from 12 to 31 days after the onset of jaundice. Peterson has previously reported that the maximal serum iron level appears after the maximal increase in serum bilirubin, which was also found in this study. The maximal rise of the serum iron probably has no relationship to the severity of the disease. However, the occurrence of the late peak in the serum iron levels may represent a more severe type of hepatitis, with prolonged convalescence, as in case 1. More investigation is needed to determine this relationship.

The peak of the iron curve may well represent the period of maximal hepatic necrosis, which has been recently shown by Reissman et al.[11] to occur in dogs. This group of investigators found that there was a direct

correlation between the pathologic changes in the dog's liver and the height of the serum iron level. Parenchymal liver necrosis in their dogs was produced by the use of carbon tetrachloride. This means of rapid production of liver cell necrosis caused a rapid rise in serum iron. There is a rapid increase in the serum iron level, beginning within 36 hours following the introduction of carbon tetrachloride into the dog's stomach. With liver cell repair there was a fall in the serum iron levels. This experimental work now tends to confirm the concept that the elevated serum iron level is associated with liver cell necrosis.

Increased serum bilirubin is not necessarily associated with elevated serum iron levels. In obstructive jaundice the serum iron levels are within normal range.

The conditions known to produce an elevated serum iron are hemosiderosis, hemochromatosis, acute viral hepatitis, diseases associated with hemolysis, such as acute hemolytic anemia with or without jaundice, and pernicious anemia. Of all the acute infectious diseases, the only one known to cause an elevation of the serum iron is acute hepatitis. No patients diagnosed as hepatitis without jaundice have been studied. This test might be helpful in clarifying this controversy.

The question raised at the beginning as to whether this test should be added to those commonly used in the so-called liver profile should be answered. From the data obtained and our clinical experience it is felt that the determination of the serum iron is definitely helpful in distinguishing between obstructive jaundice and acute hepatitis if the test is done early in the illness, and particularly if serial determinations are made. It is believed that this test is more helpful than the thymol turbidity test, which merely indicates some change in the alpha 2 and beta globulin fraction of the total proteins. The technic of performing this test is no more difficult than is that of many of the common tests done routinely in studying biochemical disturbances in liver disease. The only major apparatus necessary is a Leitz photrometer.

Conclusions

1. The serum iron level is helpful in the differential diagnosis of jaundice and should replace less specific tests.

2. Elevated serum iron levels in acute hepatitis are probably associated with liver cell necrosis.

3. The late appearance of the maximal rise of serum iron level in acute hepatitis suggests a more prolonged clinical course.

Summario in Interlingua

Le redistribution del ferro in le corpore es un processo effectuate via le sero. In iste processo le hepate ha un function importante. Studios reportate in le litteratura indica que in morbos hepatic le nivello del ferro seral es normal in patientes de cirrhosis con o sin ictero e etiam in patientes con obstructiones biliari extrahepatic. Del altere

latere, le nivello del ferro seral es elevate in casos de hepatitis acute. Iste morbo es le sol infection acute in que un tal cambiamento ha essite constatate.

Le presente reporto se basa super le studio de 61 casos de morbo hepatic demonstrate per examines histologic. In iste 61 casos, 147 determinationes del ferro seral esseva executate. In plus, 25 subjectos normal esseva studiate. In istes le ferro seral variava inter 70 e 170 μg pro cento con un valor median de 108, 4. In 34 patientes con cirrhosis le correspondente valor median esseva 102; in 10 patientes con ictero illo esseva 116. Sed in 17 patientes con hepatitis ille valor median esseva 240 μg.

Le determination del ferro seral esseva executate per un modification del methodo describite per Barkin e Walker. Nulle correlation esseva constatate inter le valores pro ferro seral e le resultatos del currente tests hepatic. Nos opina que le elevate valores pro ferro seral in hepatitis es causate per un necrosis del cellulas hepatic resultante in le retro-emission de ferro verso le sero.

Esseva registrate graphicamente le resultatos de determinationes in series del ferro seral e de altere tests hepatic executate in 2 casos seligite. Le un esseva le caso de un patiente con un prolongate convalescentia ab hepatitis. Le altere caso representava un curso typic del morbo.

Le conclusion pareva permittite que le determination del ferro seral es de adjuta in le diagnose differential de ictero. Iste determination deberea reimplaciar tests de character minus specific. Le tardive occurrentia del augmento maximal del nivello de ferro seral in hepatitis acute pare indicar un curso prolongate.

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PERIODIC PARALYSIS ASSOCIATED WITH HYPERTHYROIDISM: REPORT OF THREE CASES *

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PERIODIC paralysis, a relatively uncommon disease first reported by Musgrave [55] in 1727, has recently been reported to occur in conjunction with hyperthyroidism.

Periodic paralysis as described by Talbott [55] is characterized by intermittent attacks of flaccid paralysis of the muscles of the extremities, with loss of both deep tendon reflexes and response to electrical stimulation of motor nerves [39] without mental impairment. The paralysis begins peripherally, progressing centrally with more profound involvement of the extensor muscles of the legs than of the flexors. Rarely, the paralysis may involve the muscles of deglutition, phonation and the extra-ocular muscles causing blurring of vision. Other features are temporary bradycardia, hypotension, dilatation of the heart and increase in size of the paralyzed muscles. The paralysis may be present for from four to 72 hours, and recovery proceeds in the reverse direction to the order of onset.

Shakhnowitch [55] reported the first familial case in 1882, and approximately 80% [24] of the 450 cases reported since then were familial in type. Although the first cases were in females (Musgrave, Avarre [55]), this disease is predominantly one of males, occurring in the ratio of 3 : 1 in familial cases, and almost entirely in males in sporadic cases.

The disease occurs predominantly in young people under the age of 30, and is associated in families with muscular atrophy, migraine and epilepsy.[55] The attacks need not recur with any periodicity, and usually cease spontaneously in the fourth decade, according to Bickerstaff.[3]

A total of approximately 40 fatal cases of this disease has been reported by Neustadter,[42] MacClachen,[33] Smith,[52] Talbott [55] and McQuarrie.[36] Causes of death were cardiac failure and respiratory failure secondary to exhaustion of the diaphragm.

As early as 1901 Singer [51] and Buzzard [11] reported beneficial results from the empiric use of oral potassium salts. However, it was not until 1934 that Biemond [4] demonstrated low serum potassium levels during an episode of paralysis. This was substantiated by the reports of Ferebee,[18] Pudenz [45] and Gammon.[22] Other investigators have found a simultaneous fall in serum phosphate levels during an attack.

Allott [2] and Gass [28] have shown a decrease in the excretion of urinary potassium and phosphate prior to and during an attack. The fall in serum

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potassium has also been demonstrated by changes in the electrocardiogram consisting of prolonged QT intervals and depressed T waves, as noted by Zabriskie [61] and Stewart.[53] Levels of serum potassium as low as 1.2 mEq./L. have been reported during attacks by Allott [2] and Gass,[23] yet other attacks have occurred at levels as high as 4.8 mEq./L. This has led Gammon [22] to postulate that it is the relative decrease in serum potassium levels and not an absolute value which is the important factor. Increased urinary excretion of creatine and creatinine during an attack was also noted by Gass.[23] In contradistinction to the above authors, Tyler [58] in 1951 reported no fall in serum potassium in 33 cases of periodic paralysis during spontaneous and induced attacks.

In 1897 Goldflam [55] described the presence of characteristic vacuoles and an amorphous mass separating the central fibrils of muscle fibers taken from patients with periodic paralysis. In 1932, Brand and Harris [9] reported diminished creatine and acid-soluble phosphate content in muscle biopsies. Schoenthal [48] in 1934 showed decreased oxygen consumption by a muscle specimen taken from a patient with periodic paralysis versus normal muscle. Jantz [27] in 1947 reported doubling of the potassium content of muscle fibers during an attack as compared to that of the resting state.

Following the reports of spontaneous attacks, Putnam,[46] Kramer [28] and Shinosaki [50] showed that attacks often could be induced following the ingestion of liberal amounts of carbohydrates. Pudenz [45] reported that the administration of insulin with the carbohydrate greatly increased the likelihood of provoking an attack. Later methods for inducing attacks were the use of epinephrine by Orzechowski,[43] glucose and adrenal cortical extract by Hildebrand [25] and water diuresis by Gammon.[21]

Muscle weakness and paralysis were described in association with exophthalmic goiter (Basedow's disease) many years ago by such observers as Charcot and Mobius.[15] In 1938 Brain [8] classified these muscle manifestations as (1) acute thyrotoxic myopathy resulting in fatality due to bulbar palsy; (2) chronic thyrotoxic myopathy resulting in wasting, weakness and muscle atrophy; and (3) periodic paralysis in thyrotoxicosis.

In 1902 Rosenfeld [47] reported the first case of the association of periodic paralysis with exophthalmic goiter. Since 1902 a total of 35 cases of the association of these two conditions has been reported.[30, 50, 15, 41, 40, 35, 34, 57, 25, 49, 13, 59] Some of the larger series of these cases were reported by Shinosaki,[50] seven in 1926; Dunlap,[15] four in 1931; Tsuji,[57] eight in 1939; and Hildebrand,[25] five in 1941. Shinosaki [50] showed exacerbation of the periodic paralysis by the administration of thyroid extract. Dunlap [15] found recurrence of periodic paralysis whenever his treated cases of thyrotoxicosis relapsed. All of the reported cases, whether treated with radiation, surgery or propylthiouracil, showed disappearance of periodic paralysis when the thyrotoxicosis was cured.

In the period of 1950 to 1954, sixty-three cases of thyrotoxicosis have been treated at our institution. Of this number, four patients have shown

definite signs and symptoms of periodic paralysis. The case histories of three patients are reported below. Case one was reported in 1952 [59] and is therefore presented in abbreviated form here.

Case Reports

Case 1. A 27 year old white male of Italian descent was admitted to the Brooklyn Veterans Administration Hospital on October 21, 1950, complaining of tremors, a weight loss of 40 pounds in six months, and a two year history of periodic episodes of paralysis. Nervousness and excessive perspiration were first noted in 1945. In 1948, prominence of the left eye and episodes of paralysis of the lower extremities appeared, starting as a feeling of numbness, usually occurring at bedtime and usually preceded by a large carbohydrate meal. By morning the patient would have complete paralysis of his lower extremities, which would clear spontaneously in four to five hours. These episodes occurred three to four times a year, and the patient functioned normally between episodes. In the six months before admission these attacks occurred as often as once a month.

Review of the patient's family history failed to reveal any similar episodes of paralysis.

On physical examination the following abnormalities were noted. Obvious bilateral exophthalmos, more marked on the left, and lid lag were seen. The thyroid gland was diffusely palpable, soft and of a uniform consistency, with bruit heard over the thyroid gland. The cardiac silhouette was not clinically enlarged. Regular sinus rhythm, and a short systolic murmur heard at the apex without transmission or thrill, were noted. Blood pressure was 130/86 mm. % Hg; pulse rate on admission, 128. Fine and coarse tremors of the extended upper extremities were seen. Muscle power and tone were normal in both upper and lower extremities. Deep tendon reflexes as well as superficial reflexes were within normal limits. No abnormal reflexes were noted. Patient's skin was found to be warm and moist.

The routine laboratory studies, consisting of chest x-ray, urinalysis, serologic test for syphilis, blood sugar, cholesterol and hemogram, were within normal limits.

Initially the patient gained five pounds in weight in two weeks on bed-rest. Basal metabolic rates done during this period ranged from a low of plus 22% to a high of plus 62%. Radioactive iodine uptake studies were not available. On November 8, 1950, the patient was placed on 5 iodo-thiouracil, 300 mg. daily, which was increased to 400 mg. a day on November 21, due to lack of response to the smaller dose. The sleeping pulse rate decreased from a pretreatment level of 90 to 110, to 70 to 90, with an associated weight gain. Clinically, the patient felt improved, and repeat basal metabolic rate was plus 16%.

Following the ingestion of a heavy spaghetti dinner on the previous night, the patient developed complete paralysis of the lower extremities on the morning of December 23. He complained of inability to move his lower extremities at 2 a.m. Examination was confirmatory. There was moderate depression of the deep tendon reflexes. The remainder of the neurologic examination was within normal limits.

Blood specimen taken at that time revealed a normal blood sugar, calcium and phosphorus, with a serum potassium of 2.5 mEq. per liter. Lumbar puncture at this time was completely normal. An electrocardiogram taken during paralysis revealed lowered T-waves, with ST-segment depression and QT prolongation, compatible with hypopotassemia. This electrocardiogram was definitely abnormal when compared with previous ones. All subsequent electrocardiograms were within normal limits. Subsequent serum potassium examinations ranged from 3.9 mEq. per liter to 4.0 mEq. per liter. This attack subsided spontaneously approximately 14 hours after the onset of symptoms.

On December 29 a subtotal thyroidectomy was performed, with the removal of 80% of thyroid tissue from each side. Microscopic examination of the removed tissue revealed a diffuse goiter, showing hyperplasia with involution. Postoperatively the patient did well.

Following his recovery from the operation several provocative tests were done to induce an attack of periodic paralysis. These consisted of the ingestion of oral glu-

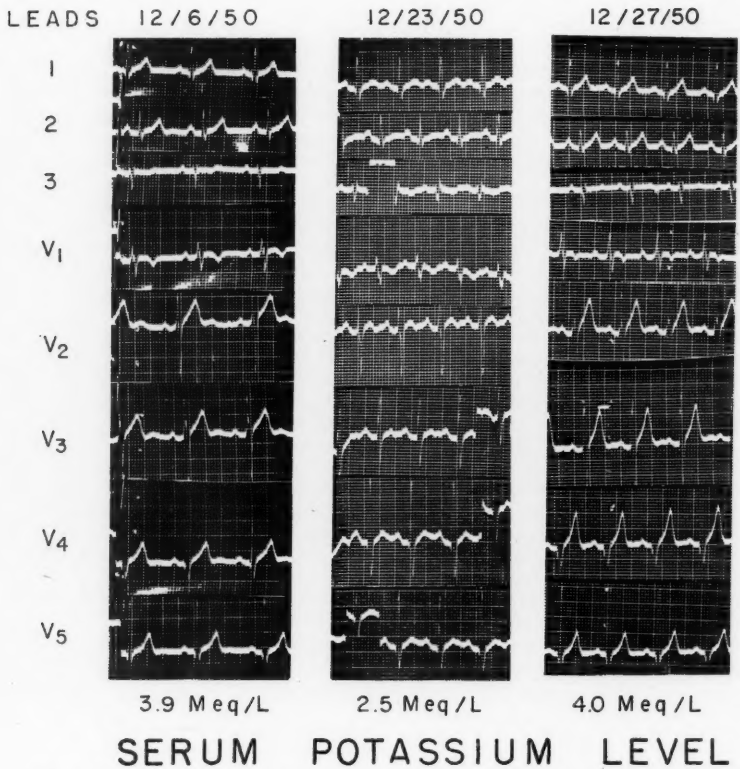

FIG. 1. *Case 1.* December 6, 1950. Asymptomatic, normal electrocardiogram and serum potassium level, December 23, 1950. Spontaneous attack of 3 to 4 plus intensity with paralysis and depressed deep tendon reflexes. Electrocardiogram showed flattened T waves and depressed ST segments compatible with hypopotassemia, serum potassium level of 2.5 mEq./L. December 27, 1950, complete recovery; asymptomatic, normal electrocardiogram and serum potassium level.

cose, 200 gm., with the administration subcutaneously of 20 units of regular insulin. At other times injections of subcutaneous doses of 0.5 c.c. of 1–1,000 dilution of epinephrine were given. None of these measures produced paralysis similar to the initial attack. Following operation the patient's basal metabolic rate remained in the range of plus 16% to plus 22% for several months.

Follow-up 40 months postoperatively reveals no history of recurrence of either hyperthyroidism or episodes of periodic paralysis. The patient has gained 47 pounds, no longer has exophthalmos, and works regularly.

Case 2. A 27 year old white married shoe salesman was admitted to the Brooklyn Veterans Administration Hospital on May 17, 1952. His illness had begun in November, 1951, with difficulty in arising from a chair after sitting for long periods

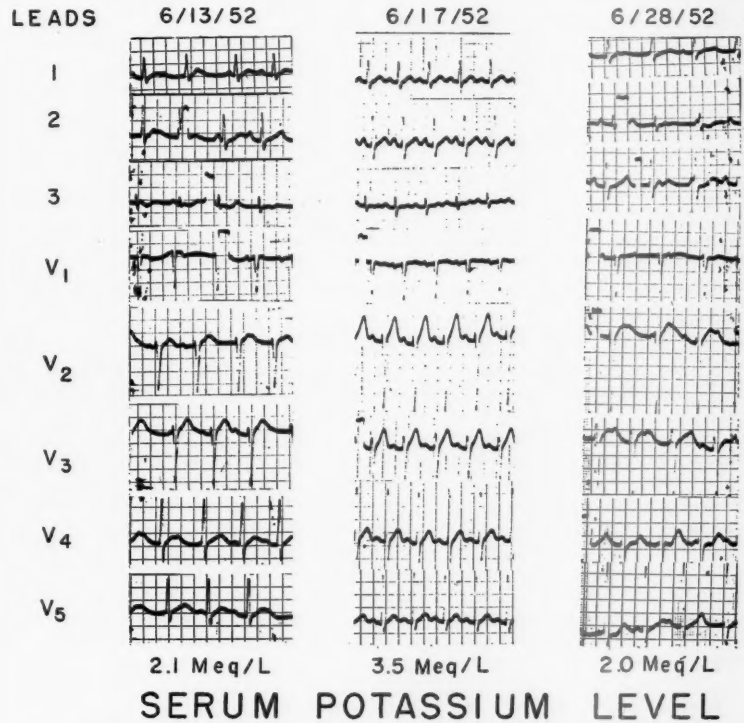

FIG. 2. *Case 2.* June 13, 1952. Attack of 3 plus severity with paralysis and almost absent deep tendon reflexes induced with oral glucose. Electrocardiogram showed second degree AV block with Wenckebach's phenomenon, flattened and prolonged T waves consistent with hypopotassemia, serum potassium level of 2.1 mEq./L. June 17, 1952. Asymptomatic, normal electrocardiogram and serum potassium. June 28, 1952. Severe 4 plus attack induced by low potassium diet and oral potassium binding resin. Electrocardiogram showed T wave changes consistent with hypopotassemia, serum potassium level of 2.0 mEq./L.

of time. Weakness, particularly of the legs and thighs, was noted. In January, 1952, the patient noted complete flaccid paralysis of both upper and lower extremities on awakening one morning at four o'clock. Between January and May, 1952, the patient had 10 similar episodes, usually occurring between 2 and 5 a.m., but never involving the muscles of the head and neck. These episodes would subside spontaneously within

four to six hours, leaving some residual weakness of the legs. Two of these episodes occurred in the last months before admission.

Previous history revealed that while the patient was in the military service he had frequently had episodes of nausea and vomiting with some epigastric distress, usually occurring between meals and relieved by the ingestion of sweets, such as chocolate. Since 1944 the patient had noted that he had become more nervous, and occasionally had tremors of the extremities. The patient also noted increasing intolerance to warm weather, and a change in his stool habits to a mild type of diarrhea, with a 20 pound weight loss in the last six months despite good appetite. A review of the patient's family history revealed no similar paralytic episodes.

On admission to the hospital the patient was suffering from the residuals of a paralytic episode which had begun at two o'clock that morning. He appeared to be well developed and well nourished. There were slight enlargement and tenderness in the area of the left lower lobe of the thyroid gland. The lungs were clear to percussion and auscultation. No cardiac enlargement, arrhythmias, murmurs or thrills were found. No abdominal viscera were palpable. The patient was unable to move his lower extremities, and muscle power in the upper extremities was diminished. There was no difficulty in swallowing. Deep tendon reflexes were markedly diminished. Plantar stimulation resulted in dorsiflexion of the right big toe without fanning and a flexor response on the left. No other abnormal reflexes were noted. Cerebellar function, sensation and cranial nerves were normal. Several hours after his admission, muscle power was restored spontaneously and deep tendon reflexes were hyperactive throughout.

Hemogram, serologic test for syphilis, serum calcium, phosphorus, urea nitrogen, chlorides, CO_2 combining power, serum cholesterol and sodium were within normal limits. A glucose tolerance test revealed a fasting level of between 75 and 110 mg.%, with a normal three hour curve. X-rays of the chest and skull, an electrocardiogram and two electroencephalograms were normal.

On the basis of the patient's history and physical examination on admission, the diagnosis of hyperthyroidism with sporadic periodic paralysis was made. Serum potassium levels drawn in the nonparalytic stage ranged between 3.55 to 6.72 mEq./L. Urinary excretion of potassium in 24 hours ranged from 74.8 to 11.6 mEq./L., and urinary excretion of creatine versus creatinine was in the ratio of 3.0 mg.% to 148 mg.%. Attempts to obtain a satisfactory basal metabolic rate were unsuccessful. Radioactive iodine uptake studies revealed a 98% uptake in the thyroid gland after 24 hours. Attempts were made to induce paralytic episodes in order to prove the clinical impression. These attempts consisted of the administration of intravenous glucose alone, and accompanied by subcutaneous regular insulin, and, at other times, subcutaneous epinephrine alone. None of these attempts resulted in muscular weakness.

On June 13, 1952, after a large supper, the patient was given 200 gm. of dextrose orally at midnight. At 6 a.m. he complained of flaccid quadriplegia. Examination revealed minimal residual muscle power in the upper extremities, with complete paralysis of the lower extremities except for the ability to move his toes. Deep tendon reflexes were markedly diminished in all extremities. Electrocardiograms revealed second degree AV block with Wenckebach's phenomenon, with rounded and prolonged T-waves compatible with hypopotassemia. Serum potassium levels at this time were 2.4 and 2.1 mEq./L. Within 12 hours of the onset of paralysis the attack subsided spontaneously with the disappearance of his abnormal electrocardiographic finding.

Following recovery from this episode the patient was placed on a diet containing 2 gm. of potassium daily, with the addition of a hydrogen cyclocarboxylic acid resin (Lilly), 8 gm. three times a day, in order to induce a low serum potassium. At 4 p.m. on the fourth day of this régime the patient noted onset of weakness of his legs which became progressively worse. Serum potassium was 2.0 mEq./L., and an electrocardiogram showed findings similar to the one done during the previous attack. The

patient was given an infusion containing 20 mEq. of potassium chloride, without dramatic benefit. He then received oral and rectal potassium, with very gradual recovery from this attack, so that the period of paralysis was prolonged to approximately 22 hours, against the usual duration of four to five hours.

The patient was given propylthiouracil, 300 mg. daily for two days, which was then discontinued because of the onset of diarrhea and pruritus. Therefore, on July 2 the patient was started on Tapazole, 30 mg. daily, and starting on August 21, Lugol's solution, 30 drops daily. These medications were continued until September 8. During this period of time the patient gained 18 pounds in weight and felt clinically improved. On September 8 he underwent a subtotal thyroidectomy. Pathologic report of the removed tissue revealed thyroid gland with hyperplasia and involution consistent with a treated case of hyperthyroidism. The patient made an uneventful recovery and was discharged from the hospital on September 30.

Follow-up 20 months postoperatively revealed that the patient had gained 38 pounds and felt perfectly well and that there had been no recurrence of any muscular weakness. Basal metabolic rate done in the summer of 1953 was within normal limits, and all signs of hyperthyroidism and exophthalmos have disappeared.

Case 3. A 25 year white male was admitted to the Brooklyn Veterans Administration Hospital on August 11, 1953. His illness had begun approximately one year before admission with an ill defined weakness of the lower extremities. In February, 1953, he had noted one morning that he was unable to move his lower extremities. This weakness persisted until noon of that day and then had disappeared spontaneously. Since that time he had had approximately 30 such episodes, about 20 of them occurring at night or in the early morning hours, when he would find he was unable to roll over in bed or to get out of bed to stand up. Some attacks occurred during the day while the patient was active. The attacks usually occurred during the night following a large evening meal, particularly one containing large amounts of carbohydrates. During the last eight months the patient had lost 40 pounds in weight despite a voracious appetite. This was accompanied by increased nervousness and irritability, with intolerance to heat, in comparison to previous summer months. No changes in bowel habits had been noted by the patient.

On August 10, 1953, an attack of paralysis of the lower extremities, and of the upper extremities to a lesser degree, began while the patient was sitting in a movie. The patient was taken to Kings County Hospital, where he received intravenous Prostigmin, without benefit, but recovered spontaneously from the paralysis. During these attacks he was conscious, rational and oriented. He stated that his extremities felt "like lead" and were painful only when he attempted to move them.

The patient appeared to be well nourished and well developed, weighing 220 pounds. Pulse, 90; blood pressure, 130/80 mm. % Hg. Examination of the patient's lungs on admission revealed musical rhonchi on inspiration throughout both lung fields. The heart was not enlarged, and no murmurs or thrills were noted. No abdominal viscera were felt. The thyroid gland was enlarged, with the greater mass on the right side. The enlarged gland moved with swallowing. No abnormality of muscle power was noted. Deep tendon reflexes were equal and active. Cerebellar functions, sensation and cranial nerves were within normal limits.

Chest and skull x-rays were within normal limits. Hemograms, serologic test for syphilis, urinalysis, blood urea nitrogen, blood sugar, serum calcium, phosphorus, alkaline phosphatase and spinal fluid chemistries were all within normal limits, including a serum cholesterol of 170 mg. %. Electroencephalogram and control electrocardiogram were normal.

On his admission to the hospital a diagnosis of hyperthyroidism was suspected. Basal metabolic rate, done with difficulty due to poor patient coöperation, gave a read-

ing of plus 27%. Radioactive iodine uptake study revealed an uptake of 67% in 24 hours, with greater concentration in the right lobe of the thyroid gland. Control serum potassium levels ranged between 4.5 and 6 mEq. per liter.

On September 16 the patient returned from pass complaining of marked weakness of the lower extremities. While on pass he had eaten a large meal consisting mostly of rice. Examination at this time revealed marked muscular weakness; however, the deep tendon reflexes were present, though diminished. There was no lid ptosis or difficulty in swallowing. Serum potassium taken at this time was 4.2 mEq. per liter. The patient recovered spontaneously from this attack. Later, an attempt was made

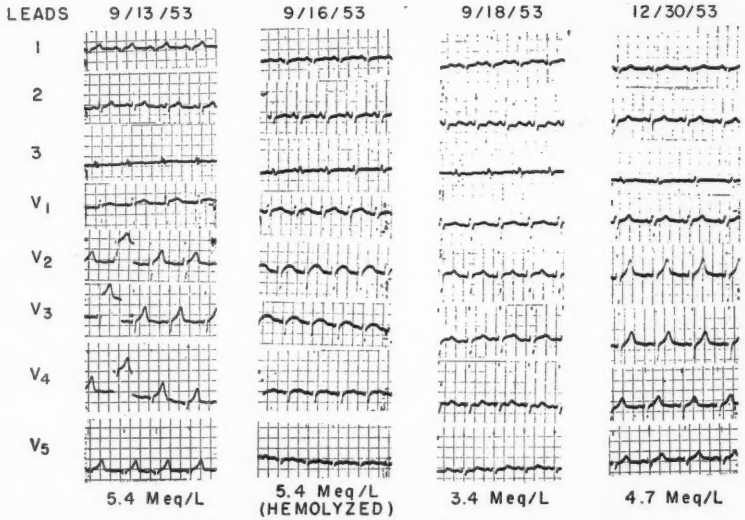

FIG. 3. *Case 3.* September 13, 1953. Asymptomatic, normal electrocardiogram and serum potassium level. September 3, 1953. Mild paralysis of legs induced with glucose and insulin. Electrocardiogram showed flattened T waves compatible with hypopotassemia. Serum potassium level was 5.4 mEq./L. However, the specimen was hemolyzed, therefore the level was inaccurate. September 18, 1953. Moderately severe paralysis induced with glucose and insulin. Electrocardiographic changes were consistent with hypopotassemia. Serum potassium level was 3.4 mEq./L. December 30, 1953. Sixteen days post-thyroidectomy, asymptomatic despite administration of glucose and insulin. Normal electrocardiogram and serum potassium level.

to duplicate the attack by administration of a high carbohydrate meal, followed by 200 gm. of glucose orally and 200 gm. intravenously, plus 50 units of insulin subcutaneously. Within five hours the patient complained of moderate weakness, with inability to stand. Although muscle strength was markedly diminished, the deep tendon reflexes were present but impaired. Serum potassium taken during this time ranged between 3.4 and 3.75 mEq. per liter, and an electrocardiogram revealed low T-waves, with depression of the S–T segment and prolonged QT interval compatible with hypopotassemia. The patient received intravenous potassium and oral potassium, with gradual increase in strength and reversion of the electrocardiogram to normal.

On September 18 the patient was started on propylthiouracil, 300 mg. per day. He received this medication for a period of 18 days. At that time he developed marked urticaria and angioneurotic edema of his hands, feet and trunk, with generalized pruritus. Propylthiouracil was discontinued, and the patient received various medications, including Pyribenzamine, and finally ACTH intravenously after he had developed swelling of his fingers and knees, periorbital edema and mild dysphagia. Within 36 hours of the institution of intravenous ACTH therapy the symptoms of the allergic phenomenon had markedly diminished.

Repeat radioactive iodine uptake studies showed an uptake of 16%. On November 2 the patient was started on Lugol's solution, 30 drops daily. Repeat administration of glucose and insulin resulted in a mild attack during which the serum potassium level was 4.1. After one month of Lugol's solution the basal metabolic rate was plus 15%, and the sleeping pulse ranged between 70 and 75.

On December 14 the patient underwent a subtotal thyroidectomy, with the removal of 130 gm. of tissue. Pathologic examination of this tissue revealed nodular adenomatous goiter with Hürthle cell changes. Recovery from the operation was uncomplicated except for persistent hoarseness.

Postoperatively (December 30) an attempt was made to induce an attack with 300 gm. of glucose orally and 50 units of insulin. This did not result in any clinical symptomatology, and a normal electrocardiogram was found six to nine hours after the glucose was given.

Ninety days postoperatively the patient had gained 38 pounds in weight, with coarsening of the skin on the dorsum of his hands and general lethargy. Radioactive iodine uptake showed an uptake of 2%, with a basal metabolic rate of minus 25%. The diagnosis of postsurgical hypothyroidism was therefore made, and the patient was started on thyroid extract, 60 mg. daily, with clinical improvement over a period of 30 days.

Another attempt to precipitate an attack of periodic paralysis resulted only in hypoglycemic symptoms, which were readily relieved by intravenous glucose. No muscle paralysis was noted.

At the present time (five months postoperatively) the patient has returned to his employment and feels well, without any spontaneous attacks of paralysis despite the intake of large carbohydrate meals.

Discussion of Mechanisms

Although it is quite clear that the level of serum potassium is related to the attacks of periodic paralysis, the exact mechanism causing the onset of the attack has never been clearly established. Many observers, including Ziegler,[63] Pudenz,[45] Gammon [22] and McQuarrie,[38] have noted prompt disappearance of symptoms after the administration of potassium, both orally and by intravenous route. Other observers (Tyler,[58] Seed [49] and Hildebrand [25]) did not find any dramatic improvement in their cases after giving potassium in comparable doses. This led Gammon [22] in 1939 to state that the fall in serum potassium is secondary to withdrawal of large quantities of potassium by muscle cells deficient in potassium; thus the fall of serum potassium follows the paralysis and does not precipitate the attack.

In support of this thesis McQuarrie,[36] Holler,[26] Black,[5] Allott [2] and Castleden [12] have demonstrated severe falls in serum potassium in such conditions as diabetic coma treated with insulin, overtreatment of Addison's

disease with desoxycorticosterone, severe acute diarrhea, and chronic nephritis without subjective or objective evidence of muscle paralysis of the severe type found in periodic paralysis.

In 1926 Shinosaki [50] explained the mechanism as a polyglandular disturbance of the glands of internal secretion, since he found definite evidence of a relationship between periodic paralysis and hyperthyroidism. In 1938 Pudenz [45] felt that the primary disturbance was in the central nervous system, since there was recovery of a paralyzed limb to which the arterial blood supply was occluded when potassium was given intravenously in another extremity. However, Gass [23] in 1948 disputed this by showing that occlusion of the blood supply to a limb leads to spontaneous release of potassium by the anoxic tissues.

There is experimental evidence relating the attacks of periodic paralysis directly to carbohydrate metabolism. Fenn [17] showed that deposition of glycogen in the liver cannot occur without the presence of potassium. Gass [23] showed that potassium acts as a catalyst, promoting esterification of inorganic phosphorus to hexose-monophosphate, which is intermediary between glucose and glycogen. These investigators, plus Talbott [55] and Danowski,[14] postulate an acute abnormal requirement of potassium during the metabolic process of glycogenesis leading to low serum potassium levels and attacks of paralysis.

On the other hand, there are observers who agree with Gammon [22] that a chronic deficiency of potassium in the muscles of these patients is the basic factor. Boyer [7] postulates that the muscles are unable to retain or mobilize sufficient potassium from endogenous sources to meet the requirements of the contractile function as well as other chemical functions. Szent-Gyorgyi [54] in 1948 showed that change in the internal ionic environment in muscle cells leads to change in the molecular form of actin so that it can no longer combine with myosin in the process of muscle contraction.

McQuarrie [36] has done extensive metabolic studies on periodic paralysis and has shown that giving a diet in which the ratio of carbohydrate to potassium is higher than 75 to 1 causes attacks of paralysis. He showed that fasting and a milk diet were beneficial in preventing attacks, whereas a high fat diet leads to many attacks.

It is our feeling that the attacks of periodic paralysis in hyperthyroidism are undoubtedly related to carbohydrate metabolism, particularly hyperglycemia, since this part of the metabolic process is most profoundly affected by an overactive thyroid. Pedersen [44] examined the serum level of potassium preoperatively and postoperatively in a large series of cases of hyperthyroidism without finding abnormal values. Hildebrand [25] felt that hyperthyroidism brings out a latent tendency toward periodic paralysis in the affected individuals. Many observers have shown prompt disappearance of attacks of paralysis with cure of the hyperthyroidism, as was demonstrated by the three cases reported here.

Summary

1. Three cases of the association of periodic paralysis and hyperthyroidism have been added to the literature.

2. Demonstration of the induction of attacks in all three individuals by the administration of glucose and insulin was shown.

3. Spontaneous absence of paralysis and inability to provoke attacks following thyroidectomy were noted in all three cases.

4. Brief resumé of the literature on mechanisms of periodic paralysis and relation to hyperthyroidism has been given.

Addendum

Following completion of this paper a fourth patient showing this symptom complex was admitted to the hospital.

A 24 year old white male with an 18 month history compatible with hyperthyroidism was admitted on September 28, 1954. The basal metabolic rate was plus 40%, and the radioactive iodine uptake was 95%. His symptoms, especially weight loss, had increased markedly from June, 1954, until admission. In June he had had a typical attack of periodic paralysis, which ended spontaneously after 11 hours. In the next three months he had approximately 10 such episodes, without loss of consciousness; the attacks always occurred in the early morning hours. In the hospital he developed marked objective weakness of his legs six hours following the administration of 200 gm. of glucose and 50 units of insulin. Unfortunately, no serum potassium level was drawn. Complete examination of the patient revealed a symptomatic left hydronephrosis due to an aberrant renal vessel. Because of the clinical necessity for rapid correction of the hydronephrosis, prompt treatment of his hyperthyroidism prevented further provocative studies of the paralytic episodes.

This patient is therefore presented as a typical clinical impression, without the confirmation of a depressed serum potassium level.

Acknowledgment

We should like to express our appreciation to the Maimonides Hospital, Brooklyn, N. Y., for the radioactive iodine uptake studies.

Summario in Interlingua

Le litteratura medical cognosce circa 450 casos de paralyse periodic, predominantemente de typo familial. Ab 1902, varie autores ha reportate 35 casos de paralyse periodic associate con hyperthyroidismo.

Ambe typos es characterisate per attaccos de flaccide paralyse, principalmente del extremitates, con un anormalmente basse nivello de kalium seral. In multe casos attaccos typic pote esser inducite per le administration de un repasto ric in hydratos de carbon, o per se o combinate con doses subcutanee de insulina o epinephrina.

Le exacte mechanismo ducente al declaration de un attacco es un question controverse. Multe theorias ha essite presentate; multes es discutite in le presente reporto. Nonobstante, le plus acceptabile theoria establi un nexo inter le morbo e le perdita o le consumption de kalium in le metabolismo glycogenic. Proque iste metabolismo es profundemente afficite per hyperthyroidismo, le postulation de un relation inter le duo entitates pare multo plausibile. In omne casos le symptomas del paralyse dispare

quandocunque le hyperthyroidismo es adequatemente sub controlo, sin reguardo al typo de therapia usate.

Es presentate 3 casos de juvene masculos adulte qui disveloppava paralyse periodic al tempore quando lor hyperthyroidismo se faceva manifeste. In iste casos il habeva nulle recurrentia del paralyse durante periodos de inter 5 e 40 menses post thyroidectomia subtotal.

Il existe un forte probabilitate que le duo mentionate entitates coexiste plus communmente que previe reportos ha indicate.

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MYCELIAL FORMS OF *COCCIDIOIDES IMMITIS* IN SPUTUM AND TISSUES OF THE HUMAN HOST *

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For half a century it has been known that *Coccidioides immitis* ordinarily exists in two distinct phases, the saprophytic and the parasitic, the former occurring in external nature and culture media, and the latter, in animal tissues. The biphasic life cycle of the fungus was first outlined by Ophüls,[1] and was more extensively delineated by Baker, Mrak and Smith.[2]

The usual life cycles of the fungus are as follows:

Parasitic Cycle: The injected or inhaled arthrospore or chlamydospore becomes rounded and shows the doubly refractile walls of the spherule or sporangium. Its protoplasm divides by cleavage planes to form endospores, which are liberated by rupture of the spherule walls. This cycle may be repeated indefinitely within host tissues as the endospores develop into mature sporangia and rupture once more, liberating a new generation of endospores.

Saprophytic Cycle: The parasitic phase is terminated and the saprophytic phase begun by the death of the host or by the expulsion of the spherule from the host's body in sputum or pus. In the external environment, germ tubes extrude from spherule walls to produce hyphae or mycelia, which are at first undifferentiated. Mature, septate hyphae are composed of arthrospores and increasingly numerous chlamydospores. In its mycelial phase the fungus may be able to perpetuate itself indefinitely until its spores enter the animal body, whereupon the parasitic phase supervenes.

The distinction between the two phases is, however, not absolute. Under certain circumstances, spherules are produced in culture media. As early as 1914 MacNeal was able to perpetuate spherule multiplication in pus by mixing it with ascitic fluid or horse serum containing sterile kidney slices.[3] In 1938 Lack caused spherules to appear in the saprophytic cycle by altering the environment of the mycelial elements, i.e., by semianaerobic incubation of chlamydospores in glucose broth and partially coagulated egg albumin.[4] In 1941 Baker and Mrak observed "culture spherules" in old cultures of certain strains of *C. immitis*.[5] Newer methods of propagating spherules in vitro have been described by Burke,[6] Lubarsky and Plunkett [7a] and Conant and Vogel.[7b]

*Received for publication January 29, 1955.

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Dennis and Hansen have recently described the growing of spherules in living tissue cultures.[8] In their perfusion type culture chamber both spherules and hyphal forms were produced at the same time, i.e., the saprophytic and parasitic cycles occurred side by side, with interconversion one to the other.

The demonstration of spherules in the saprophytic cycle showed that the two phases of *C. immitis* are not necessarily mutually exclusive. Its life cycle is not composed of obligatory phases, like—for instance—those of certain flukes. The fungus exists in varied forms merely because it reacts to different environments in different ways. In the cultural conditions of the animal body, sporangia and endospores develop. In the more meager environment of the laboratory culture plate, hyphae and hyphal spores appear, forms which are hardier, but which are less economical from

TABLE 1

Types of Coccidioidomycosis

I. Primary coccidioidomycosis
   A. Asymptomatic
   B. Symptomatic
      1. Influenza-like syndrome
      2. Pneumonia
         (a) With pleural effusion
         (b) With acute cavitation
   C. Residual pulmonary lesions
      1. Chronic cavitation
      2. Coccidioma (pulmonary granuloma)
      3. Fibrosis
      4. Bronchiectasis

II. Disseminated coccidioidomycosis (coccidioidal granuloma)
   A. Acute fulminating dissemination
   B. Chronic dissemination
   C. Meningitis
   D. Isolated peripheral granuloma

the standpoint of reproduction. Alteration of laboratory conditions, however, results in the appearance of sporangia in cultures. The long-unanswered question was whether unusual conditions ever brought about the appearance of mycelial forms in the animal host.

It was formerly thought that the only absolute difference between the two phases was the failure of the fungus to produce mycelia in living tissue. As Baker, Mrak and Smith concluded from their classic study of 1943, "The essential difference between the complete cultural cycle (with cultural spherule production) and the parasitic cycle is the complete absence of hyphal development in the latter." [2]

In the past several years there have been sporadic accounts of the discovery of mycelial elements in coccidioidal pulmonary cavities. Although the possibility of this unusual finding is well recognized by those who regu-

larly see cases of coccidioidomycosis, it is apparently not appreciated in other medical circles. We have seen a valid diagnosis of coccidioidomycosis temporarily doubted by experienced pathologists because hyphae were found in the tissues. It is the purpose of this paper to bring to general attention the frequent occurrence of mycelia in the tissues and discharges of patients with certain types of coccidioidal disease.

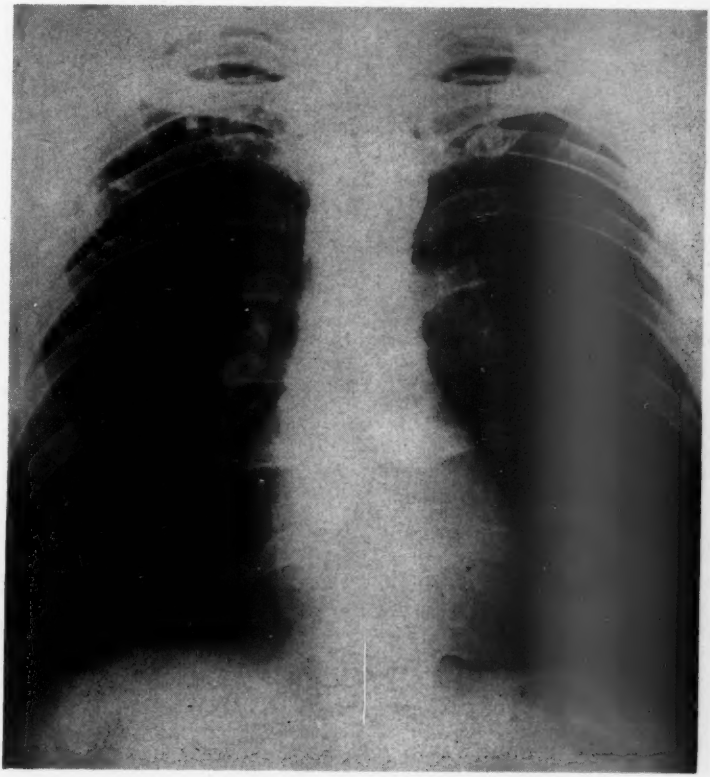

FIG. 1. Roentgenogram of the chest of a patient with a thin-walled coccidioidal cavity in the apex of the right lower lobe. Both spherules and mycelia of *C. immitis* were found in the sputum and in the surgically resected lesion.

Coccidioidomycosis occurs in several forms, in each of which the implications and seriousness are different (table 1). Primary infections severe enough to cause patients to seek medical care are most often attacks of acute coccidioidal pneumonia. The vast majority of such infections subside spontaneously after several weeks, leaving only a positive skin test

and permanent immunity as sequelae. The important complications of primary coccidioidomycosis are: (a) dissemination, and (b) residual pulmonary lesions. In about 0.2% of the cases in Caucasians, and in at least 10 times as many cases in the dark-skinned races, the infection becomes disseminated to the skin, subcutaneous tissue, viscera, bones and central nervous system, a catastrophe fatal in about 50% of those affected. A much less

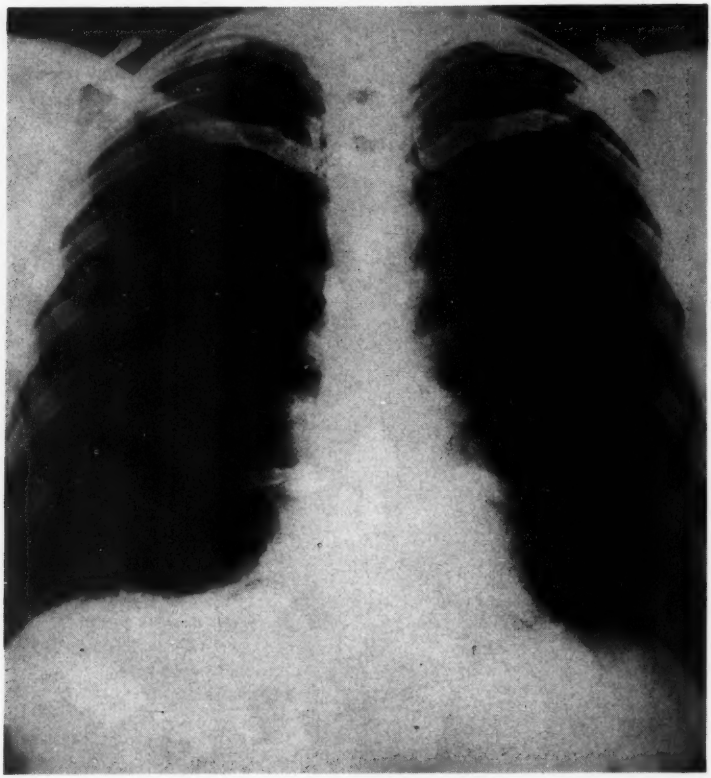

FIG. 2. Roentgenogram of the chest of a patient with an asymptomatic, accidentally discovered coccidioidal granuloma of the apex of the left lower lobe. Mycelia, but no spherules, of *C. immitis* were found in the surgically resected lesion.

serious complication of primary coccidioidal pneumonia is the persistent pulmonary lesion, i.e., a cavity or a granuloma (figures 1 and 2). The incidence of this complication can be only roughly inferred, but it appears that cavities develop in from 2 to 8% of symptomatic primary infections.[9] In Caucasians it is therefore a much more common complication than is

the dread disseminated form of the disease. The persistent pulmonary cavity and pulmonary granuloma are to be sharply distinguished from disseminated coccidioidomycosis, formerly called "coccidioidal granuloma." Residual pulmonary lesions, not prone to dissemination, become important only if cavities bleed, rupture or become secondarily infected, or if granulomas cannot be distinguished roentgenographically from neoplasms. An incidental characteristic of cavities and granulomas which distinguishes them from all other types of coccidioidal disease is their tendency to harbor *C. immitis* in its mycelial phase. Only recently has this unique proclivity been appreciated.

In 1946 Forbus and Bestebreurtje reported that in one of their 95 cases of coccidioidomycosis studied pathologically a huge pulmonary cavity contained hyphae but no spherules.[10] The identity of the fungus was demonstrated when *C. immitis* was cultured from the exudate. In the same year Barnes, formerly of Fitzsimons Army Hospital, reported a patient whose large coccidioidal cavity contained clumps of mucoid material in which were found mycelia and spherules.[11] Smith, Beard and Saito noted in 1948 that "in two patients at Fitzsimons General Hospital and one at Baxter General Hospital coccidioidal cavities removed surgically were observed to contain coccidioides in mycelial forms." [9] In two papers presented in 1949 from Fitzsimons Army Hospital, Greer discussed nine patients who had undergone lobectomy for persistent coccidioidal cavities. In the specimens from six of the nine patients the mycelial form of the fungus was observed. Three of these specimens also contained the spherule form. Three others contained only spherules.[12, 13] In the discussion of Greer's paper, Raine mentioned another case in which hyphae were found in a coccidioidal pulmonary cavity.[14] Weisel and Owen reported the same case in greater detail.[15] In 1950 Rosenthal mentioned, on the basis of personal communications, that the vegetative forms of the fungus are occasionally found in large pulmonary cavities, but he cited no new examples.[16] Smith wrote in 1950 that "mycelia have been found in the cavities of some patients, but this is not remarkable inasmuch as the situation there is much like that encountered in the external environment." [17] In 1953 Guilfoil also reported the finding of mycelia as well as spherules in the specimen of one of three patients who underwent lobectomy for coccidioidal cavities.[18]

In 1954 Seabury, Peabody and Liberman, in describing the value of the Hotchkiss-McManus stain, reported a case of coccidioidomycosis in which mycelial forms were found by restaining slides after this method.[19] Reviewing the pathologic material at the Fitzsimons Army Hospital, Puckett in 1954 found hyphae of *C. immitis* in 73% of 34 cavities and in 30% of 30 pulmonary granulomas.[20] He did not report the demonstration of hyphae in the sputum, although he pointed out the probability that some cavities communicate with the bronchial tree and inferred that "the expectoration of infective mycelial elements may occur occasionally."

As far as we know, all of the reports of mycelial forms in human tissues have concerned pulmonary cavities and granulomas, with one questionable exception.* The finding of hyphae of *C. immitis* in the sputum has not previously been described. In this paper we report the demonstration of mycelial forms in the sputum as well as in the pathologic specimens of patients with coccidioidal lesions of the lung.

Material and Methods

Ninety-eight cases of coccidioidomycosis have been studied at the Fresno Veterans Administration Hospital since it was activated in March, 1950. Twenty-four of these were cases of disseminated coccidioidomycosis and 17 were cases of persistent pulmonary lesions without dissemination (nine cavities and eight granulomas). Sixty-eight were cases of primary pulmonary coccidioidomycosis when first observed, but dissemination occurred later in 10, and pulmonary cavitation in one. Pulmonary resection or lobectomy was done in 12 cases, eight times for cavity and four times for granuloma.

Mycologic Methods

1. *Slides and Stains:* Histologic slides were prepared by routine section of paraffin blocks. Sputum slides were prepared by smearing selected material from fresh specimens on the surface of standard slides and immediately fixing them in alcohol and ether (equal parts of 95% ethanol and anesthetic ether). Slides were stained according to the periodic acid-Schiff technic of Hotchkiss and McManus.[19, 22] This procedure is based on the fact that certain pathogenic fungi contain carbohydrates, mucoproteins and glycoproteins which are oxidized by periodic acid to aldehydes, which are in turn colored by the Schiff reagent. In several cases another staining technic was also used, a technic being adapted in this laboratory to the study of *C. immitis* (figures 4 and 5). Parker 51 Super Chrome Blue Black Ink has been reported to be useful in staining spirochetes and certain pathogenic fungi of skin.[23, 24, 25] We have found that both spherules and mycelial forms of *C. immitis* are beautifully demonstrated on slides stained with this ink and counterstained with eosin. A more complete description of this new procedure will be published elsewhere.[26]

2. *Culture Methods Used in Isolation and Identification of* C. immitis: (a) Initial cultures were made by streaking sputum on Sabouraud's dextrose agar (Difco), to which was added penicillin (20 units per milliliter), streptomycin (40 units per milliliter), and Acti-dione (0.1 mg. per milliliter). This medium, originally described by Georg, Ajello and Gordon,[27] selectively allows *C. immitis* to grow while inhibiting bacteria and other fungi.

(b) Identification of cultures was made as follows: When the early,

* Joress and Bushueff in 1952 reported a case of disseminated coccidioidomycosis in a Negro in which a gastric washing "showed rocket-shaped mycelial organisms resembling *Coccidioides immitis*." [21]

still moist colonies of *C. immitis* were first seen, samples were transferred by a wire loop to screw-capped tubes of Brain Heart Infusion Broth (Difco). The Sabouraud plates were then immediately sealed with masking tape and were set aside for further observation of the cultural and morphologic characteristics of the colonies. When growth became apparent in the BHI Broth after six to 10 days, it was emulsified by vigorous shaking. Then 0.2 ml. of the emulsified broth culture was inoculated into the testicle of a male guinea pig weighing at least 250 gm. When a definite abscess could be felt, after six to 10 days, the guinea pig was sacrificed or the testicle was removed under ether anesthesia. The identification of the fungus was completed by recovering from the abscess the typical endosporulating spherules of *C. immitis*.

The culturing of *C. immitis* in the laboratory is generally considered to be a hazardous procedure because of the ease with which the dry hyphae of mature colonies are disseminated throughout the atmosphere. We have

TABLE 2

The Incidence of Spherule and Mycelial Forms of *C. immitis* in the Sputum and Pathologic Specimens of 16 Cases of Residual Coccidioidal Pulmonary Lesions

Type of residual lesion	Cavity	Granuloma
Total number of cases	9	7
Number undergoing pulmonary resection	8	4
Number with *C. immitis* demonstrated in the sputum	8	0
Positive culture	8	0
Spherules	4	0
Mycelia	4	0
Number with *C. immitis* demonstrated in the pathologic specimen	7	4
Spherules	7	3
Mycelia	3	3

found that the danger is negligible when the above described method is followed. Transfer is made from the solid to the liquid medium before airborne hyphae develop, and the original culture plate is then permanently and tightly sealed. None of our laboratory personnel has become infected since this procedure was adopted.

FINDINGS

Sputum examinations were done in all cases of pulmonary cavitation (except in that of a young man whose complicating pneumothorax required immediate surgical intervention), and in those cases of granuloma in which sputum could be produced. In all cases of cavitation, with the exception noted, cultures were positive for *C. immitis* (table 2). In addition, spherules were seen in direct smears of the sputum in four cases, and mycelia in four. In one case no spherules could be found in the sputum on repeated search, but mycelia were frequently seen, the culture was positive, and intra-

testicular inoculation of a guinea pig produced lesions from which spherules could be obtained. In three other cases both spherules and mycelia were seen in the smear, and in one only spherules were seen. In none of the cases of pulmonary granuloma was the fungus found in the sputum, by either smear or culture. Most of the patients could not produce enough sputum to study properly. In four cases of solid pulmonary lesions which were not explored surgically, the presumptive diagnosis of coccidioma was based on the roentgenographic findings, the positive complement fixation tests, and positive coccidioidin skin tests.

In three of the eight cavities and in three of the four granulomas which were removed surgically the mycelial forms of *C. immitis* were discovered. In two of these cases the original diagnosis had been "granuloma of unknown cause" because no organisms were found on slides routinely stained with hematoxylin and eosin. When the specimens were restained after the method of Hotchkiss and McManus, the hyphae of *C. immitis* were nicely demonstrated in one, and the spherules in the other. In another case *C. immitis* was cultured from a resected granuloma, but no organisms were seen until the sections were restained with the Hotchkiss-McManus stain, whereupon both spherules and mycelial fragments were found.

Because the surgical procedure was sometimes done in other hospitals or before our study was undertaken, the original pathologic material was not always available to us for review. Although we were able to obtain slides and paraffin blocks of these specimens, the sections had not been taken from the areas most suitable for our purposes. As a matter of fact, we were able to demonstrate mycelial forms in cavities only in the three cases in which we had the whole pathologic specimen available. In the five cases in which we had only tiny sections to study, no hyphae were seen. In one of these, hyphae were abundantly present in the fresh sputum, so that they must also have been present in the lungs, had the proper area been examined. Mycelia are most likely to be found on the surface of cavity walls and in the necrotic debris within granulomas.

Case Reports

Case 1. A 33 year old white farm laborer entered because of recurrent fever and hemoptysis for seven years. The roentgenogram of the chest showed several thin-walled cavities in the apex of the left upper lobe. The complement fixation titer for coccidioidal infection was positive at 1:2.* On microscopic examination, freshly obtained sputum was seen to contain many mycelial elements as well as spherules (figure 3). *C. immitis* was cultured from the sputum. Left upper lobectomy was done at another hospital. Spherules were seen on microscopic examination of a slide stained with hematoxylin and eosin, but no hyphae were observed.

We were able to obtain the slides and a paraffin block for restaining with Hotchkiss-McManus stain, but unfortunately the section had not been taken from

* Facilities for the serologic tests were provided by the support of the Commission on Acute Respiratory Diseases of the Armed Forces Epidemiological Board at the School of Public Health, University of California, Berkeley.

the part of the specimen most likely to contain hyphae. No mycelial elements were seen.

Case 2. Four years after an attack of primary coccidioidal pneumonia a 24 year old white tractor driver entered because of recurrent productive cough. Roentgenograms of the chest showed numerous densities in the right middle and lower lobes.

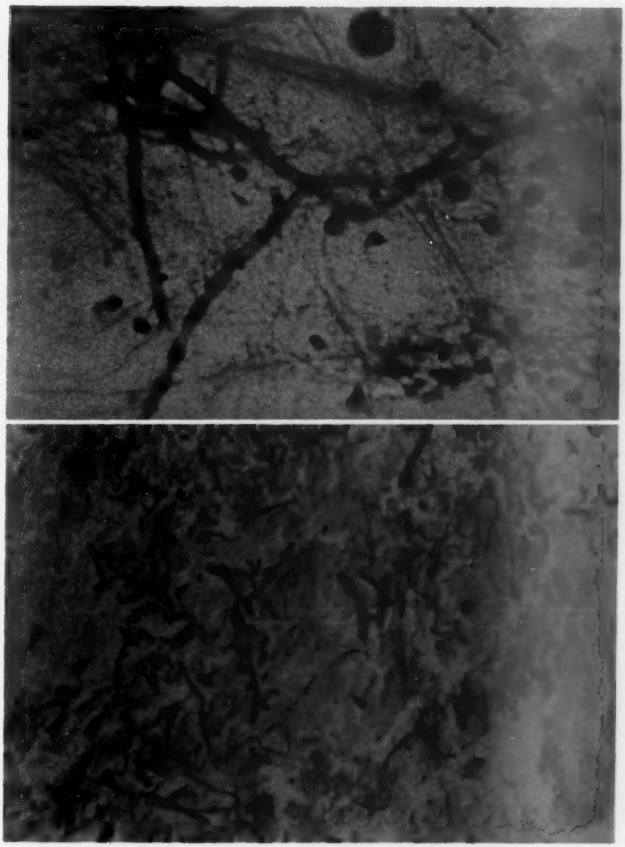

FIG. 3. (*Above*) Branching septate hyphae of *C. immitis* in fresh sputum of a patient with a coccidioidal cavity of the lung. (Hotchkiss-McManus stain. High dry.)

FIG. 4. (*Below*) Mycelia of *C. immitis* in bronchial plug from resected lung of a patient with coccidioidal bronchiectatic cavities. (Parker ink-eosin stain. Low power.)

The complement fixation titer for coccidioidal infection was positive at 1:64. On microscopic examination, many fresh specimens of sputum were seen to contain mycelia, but no spherules could be found. *C. immitis* was cultured from the sputum. Typical spherules of *C. immitis* were obtained after intratesticular injection of culture

material into a guinea pig. Segmental resection of the diseased lobes was done, showing large bronchiectatic cavities filled with grayish green material. Microscopic examination of the bronchial plugs showed large numbers of mycelial elements (figure 4). The adjacent lung parenchyma contained a few spherules of *C. immitis*.

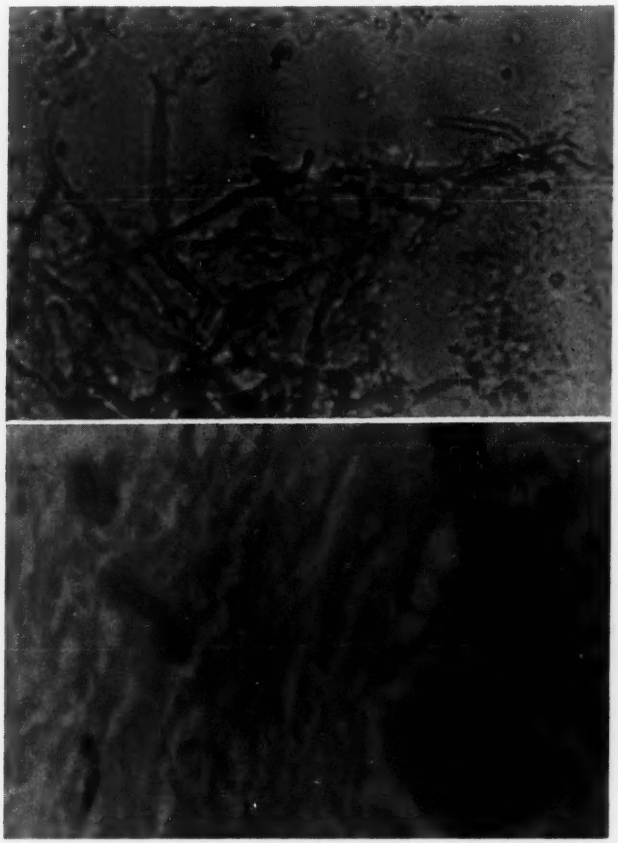

FIG. 5. (*Above*) Branching septate hyphae of *C. immitis* scooped from wall of a freshly resected coccidioidal cavity. (Parker ink-eosin stain. High dry.)
FIG. 6. (*Below*) Mycelial elements and endosporulating spherule of *C. immitis* in a coccidioidal granuloma. (Hotchkiss-McManus stain. High dry.)

Case 3. A 39 year old white farm laborer entered because of hemoptysis and weight loss for three months. The roentgenogram of the chest showed an irregular, thin-walled cavity in the apex of the right lower lobe (figure 1). Microscopic examination of fresh sputum showed many mycelial elements and spherules. *C. immitis* was cultured from the sputum. After intratesticular inoculation of the

material into a guinea pig, typical spherules of *C. immitis* were recovered. The complement fixation test for coccidioidal infection was negative. Segmental resection of the excavated lobe was performed, showing a cavity with a ragged, reddish brown surface. Microscopic examination of the wall of the resected cavity showed both mycelia and spherules.

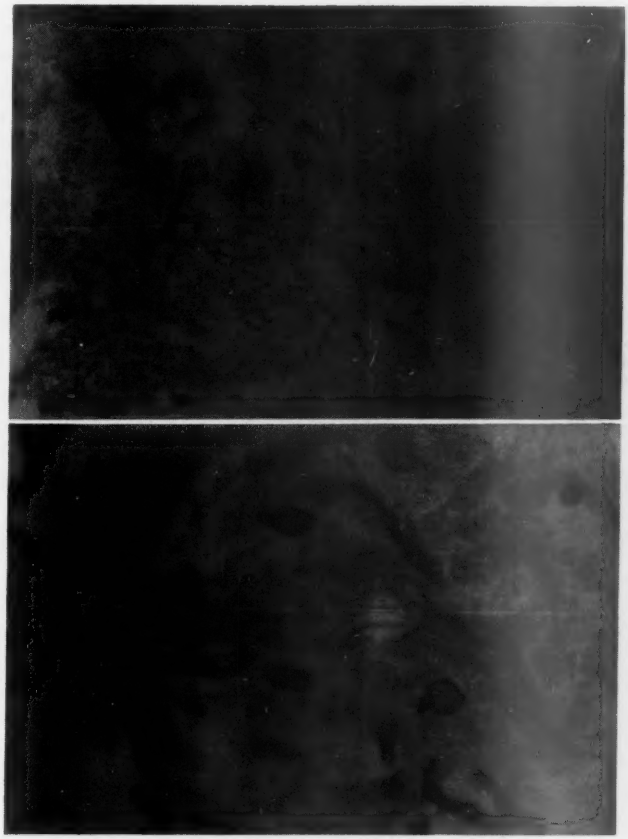

FIG. 7. (*Above*) Hyphae of *C. immitis* discovered on restaining a section from an "undiagnosed granuloma." (Hotchkiss-McManus stain. Low power.)
FIG. 8. (*Below*) Same specimen as figure 5. (Hotchkiss-McManus stain. High dry.)

Case 4. A 26 year old white shipping clerk entered because of recurrent hemoptysis. A year previously an attack of primary coccidioidal pneumonia had been complicated by a bleeding cavity of the right upper lobe, for which segmental resection was done. After nearly a year of good health, hemoptysis recurred. Roentgenograms showed cavities in the left upper lobe and in the apex of the re-

maining right lung. Spherules and mycelial fragments of *C. immitis* were found in direct smears of the sputum, and a culture was positive for the fungus. The complement fixation titer for coccidioidal infection was positive at 1:256.

After a period of unsuccessful conservative therapy, resection of the remaining right upper lobe and adjacent segments of the right middle lobe and right lower lobe was performed. In the right lower lobe there was a 3 cm. thin-walled cavity, its lumen lined by a shaggy tan substance which, when scooped off and examined under the microscope, was seen to be tangled hyphae of *C. immitis* (figure 5). Histologic sections of the lung showed many granulomatous areas containing spherules of *C. immitis*.

Case 5. A 56 year old white warehouseman entered the hospital for investigation of an asymptomatic pulmonary lesion discovered by routine roentgenographic examination. He had lived in the San Joaquin Valley for several years but recalled no respiratory illnesses. The roentgenogram of the chest showed a round density, 2 cm. in diameter, in the apex of the left lower lobe. To rule out the possibility of tumor, the nodule was removed surgically. The lesion was composed of necrotic fibrous tissue containing birefringent endosporulating spherules and abortive hyphae (figure 6).

Case 6. When she was hospitalized for an unrelated condition a 33 year old white housewife was noted to have an abnormal chest roentgenogram. She had lived in the San Joaquin Valley for years but had never had any respiratory symptoms. Sputum examination was negative. Roentgenographic examination of the chest showed a 4 cm. spherical mass in the apex of the left lower lobe (figure 2). The complement fixation titer for coccidioidal infection was positive at 1:2. Thoracotomy and excision of the mass were performed. The lesion proved to be a large granuloma filled with caseous material. No fungi or tubercle bacilli were found on routinely prepared slides, so that a diagnosis of "chronic granuloma of unknown cause" was made. When our study was undertaken the slides were restained after the method of Hotchkiss and McManus and showed mycelial forms of *C. immitis* (figures 7 and 8). No spherules were noted.

Case 7. A 57 year old white farm laborer entered because of a cough productive of scanty white sputum for a month. Many sputum examinations were negative for fungi. The roentgenogram of the chest showed a round mass in the middle of the right upper lobe. The complement fixation test for coccidioidal infection was negative. Segmental resection of the apical and posterior segments of the right upper lobe was performed. In the specimen was a nodule 2 cm. in diameter, a densely encapsulated lesion filled with necrotic debris. No fungi were seen, but culture of the material produced a heavy growth of *C. immitis*. When the sections were restained with the Hotchkiss-McManus stain, numerous spherules and rare mycelial elements of *C. immitis* were observed.

Discussion

The demonstration of hyphae in certain host tissues does not necessarily invalidate the concepts that the vegetative and parasitic phases of *C. immitis* are ordinarily distinct. Mycelia appear in the animal body only under conditions which approximate those of the external environment. The surface of a pulmonary cavity is more like the surface of an artificial culture medium than it is like the parenchyma of lung, the meninges or the spleen. It is not remarkable that mycelia should grow in such a cavity, or that hyphae should be found in its discharges. Furthermore, it is known that some granulomas

develop from thin-walled cavities. Winn reported that in 6% of his series of 92 cases the cavity became filled and formed a persistent nodule.[28] Serial roentgenograms now and then record the evolution of an empty cavity into a cavity with a fluid level, and then into a solid spherical lesion which, when removed surgically, proves to be a coccidioidal granuloma. Hyphae are most likely to be found, not in living tissue, but on the surface of a cavity or in the necrotic debris of a granuloma.

Forms of *C. immitis* which occur outside of their natural habitat are often atypical. Spherules which appear in cultures are smaller, on the average, than those in tissues. Conversely, the hyphal forms seen in human tissues are likely to be abortive and immature, often without normal segmentation, mature arthrospores or chlamydospores. Puckett[20] has described "intercalary culture spherules," like those of Baker and Mrak,[5] occurring between hyphal elements in a pulmonary cavity.

Mycelial forms will be found with increasing frequency in tissues and discharges when the search is made in the right place with adequate stains. One rewarding method is to open the freshly resected cavity immediately, scoop out a bit of the material on the surface of its wall, stain it with fountain pen ink, and examine it without delay. Tissue preparations may be stained either by the method of Hotchkiss and McManus or by the ink method described herein.

The Problem of Contagiousness of Coccidioidomycosis

Ever since the first demonstration of mycelial forms of *C. immitis* in pulmonary tissues, the question of man-to-man transmission has been discussed.[16, 29] On the basis of pathologic study of a case or two, some writers have concluded that coccidioidomycosis must be considered a contagious disease.[13, 15, 19] Fear of communicability has been expressed, not by writers who live in the endemic area, but by those who live elsewhere and who therefore see only sporadic cases.

The finding of hyphae in the sputum raises the question of contagiousness even more poignantly than does the demonstration of mycelia in pathologic sections of pulmonary tissue. The theoretic danger is nevertheless challenged by the complete lack of evidence of "contact infection" in the experience of those who deal constantly with this disease.[9, 28] In the most extensive study to date of hyphal forms in human tissues, Puckett concludes that "if hyphae are expectorated, 'contacts' of patients with coccidioidomycosis have not been harmed by them in the past."[20] Although there are always several patients with coccidioidomycosis on our wards, we have never yet seen evidence of interhuman transmission of the disease. In our experience, the man in the bed next to that of a patient with a coccidioidal cavity is very much safer than the transient farm laborer exposed to the dust of an endemic area. The risk of the former is incomparably less. In 1950 Smith wrote that the presence of mycelia in pulmonary cavities "might give one pause

with respect to the isolation of such patients. However, apparently the output of the fungus is so small that it still does not pose a problem." [17] The ease with which hyphae were found in the sputum of some of our patients may mean that the output is not always small, but there is still no clinical evidence of man-to-man transmission. Ordinary hygienic precautions are, in our opinion, all that is indicated in the care of patients with coccidioidal pulmonary cavities.

The only type of coccidioidal disease in question is the persistent pulmonary cavity or granuloma. Mycelia do not occur in such other forms of the infection as primary coccidioidal pneumonia and disseminated coccidioidomycosis. Even if the theoretic hazard of transmission from a patient with a cavity should some day be realized, this finding would have no implications whatever regarding other types of the disease. We once transferred a patient with disseminated coccidioidomycosis to a hospital near his home, only to learn that there he was isolated so energetically that he was all but abandoned by the terrified staff. Inasmuch as his freedom at our hospital had been unlimited, we could appreciate his confusion at finding himself suddenly banished from society. Such unnecessary precautions bespeak only ignorance of the disease.

The staff of the Fresno Veterans Administration Hospital is composed in large part of personnel who have only recently come to the San Joaquin Valley, and who are therefore not immune to coccidioidal disease. The combined exposure of staff members to infected patients represents a total of several hundred exposure-years. Nevertheless, there has been only one known case of primary coccidioidomycosis among hospital personnel—that of a nurse who contracted the disease during the peak of the coccidioidomycosis season, just as any newcomer to this area might.

Whatever the theoretic hazard of communicability of coccidioidomycosis, the practical hazard is so insignificant that, except for ordinary precautions, it can safely be disregarded. Even despite our discovery of coccidioidal hyphae in the sputum of patients with pulmonary cavities, clinical evidence is overwhelmingly convincing that coccidioidomycosis is not ordinarily a contagious disease.

Summary and Conclusions

1. Mycelial forms of *C. immitis* were demonstrated in the sputum of four patients with coccidioidal cavities of the lung. This finding has not been previously reported.

2. In a series of 12 cases of persistent pulmonary coccidioidal lesions which were removed surgically (eight cavities and four granulomas), mycelial forms of the fungus were demonstrated in the pathologic specimens of six (three cavities and three granulomas).

3. Mycelial forms are most likely to be found on the surface of the wall of a cavity or within the necrotic debris of a granuloma.

4. Hyphae are often easily demonstrated when other methods fail by the use of the Hotchkiss-McManus stain or by the use of a procedure, described herein, using fountain pen ink.

5. Despite the theoretic hazard of mycelia in the sputum, contagiousness of coccidioidomycosis has not been demonstrated.

ACKNOWLEDGMENT

The photomicrographs in figures 4–8 were through the courtesy of Dr. James A. Mattison, General Hospital of Fresno County, Fresno, California.

SUMMARIO IN INTERLINGUA

Le microorganismo *Coccidioides immitis* existe usualmente in duo phases: (1) Le phase saprophytic in que illo se presenta como un massa mycelial de hyphas in le natura externe o in medios de cultura; e (2) le phase parasitic in que illo se presenta como un spherula endosporulante in invadite texitos animal. Sub certe conditiones le forma spherular es observate in medios de cultura artificial, sed usque recentemente le forma hyphal non esseva unquam observate in texitos del hospite. Le prime exceptiones de iste regula esseva le recente recognition de elementos hyphal de *C. immitis* in duo typos benigne de residue lesiones pulmonar: (1) Chronic cavitation e (2) chronic granuloma o coccidioma. In le presente reporto le autores publica le prime observation de elementos hyphal de *C. immitis* non solo in specimens pathologic sed etiam in le sputo de patientes con chronic cavitationes.

In un serie de 12 patientes con persistente lesiones coccidioidal pulmonar (8 cavitates e 4 granulomas), formas mycelial de *C. immitis* esseva demonstrate in 6 del specimens pathologic obtenite al operation (3 cavitates e 3 granulomas). Formas mycelial del organismo esseva etiam observate in le sputo de 4 del patientes con cavitates. Nulle previe reporto de un tal observation esseva trovate in nostre scrutinio del litteratura.

Formas mycelial de *C. immitis* se trova le plus facilemente al superficie del pariete cavitari o intra le massa necrotic de un granuloma. Le identification de hyphas es frequentemente facilitate—mesmo in caso de non-successo de altere methodos—per medio del tinctura de Hotchkiss-McManus o per medio de un technica a tinta a scriber le qual es describite in le presente reporto. Theoricamente le presentia de *C. immitis* in le sputo constitue un risco, sed in le practica nulle contagiositate ha unquam essite demonstrate.

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THE RESULTS OF 2-HYDROXYSTILBAMIDINE THERAPY IN DISSEMINATED COCCIDIOIDOMYCOSIS *

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THE treatment of disseminated coccidioidomycosis has been unsatisfactory. In its progressive or meningitic form the disease has been uniformly fatal, although some cases have lingered on for a long time. In recent years an increasing number of reports have appeared dealing with the promising results of treatment of certain disseminated mycotic infections with stilbamidine. Arrest of blastomycosis by stilbamidine therapy can now be accepted.[5, 6, 7, 14, 15, 16, 19, 23, 25, 26] Successful treatment of actinomycosis has been reported.[12] The efficacy of the drug in the treatment of other mycotic diseases, however, seems doubtful.[13, 14]

In vitro studies with stilbamidine have demonstrated an inhibitory effect on the growth of *Coccidioides immitis*.[3, 20] The in vitro concentration of the drug necessary for inhibition is high, of the order of 50 mcg./c.c. of medium. In addition, the administration of stilbamidine is followed by the complication of a troublesome trigeminal neuropathy which limits the total dose of drug that can be given.[1, 17, 18] It was therefore decided to test the influence of a stilbamidine derivative, i.e., 2-hydroxystilbamidine, upon the course of coccidioidomycosis. Favorable results obtained with 2-hydroxystilbamidine in the treatment of blastomycosis have been reported previously.

The 2-hydroxy compound does not cause neuropathy, and even in high dosage no serious toxicity has been observed to date.[21, 22, 25, 26] It was hoped that because of the low toxicity of 2-hydroxystilbamidine, permitting administration of a much greater total dosage, the therapeutically necessary tissue concentrations of the drug would be attainable and would thus influence the course of the coccidioides infection. Only one case report has come to the attention of the authors on the treatment of coccidioidomycosis in the human with either stilbamidine or 2-hydroxystilbamidine. This patient received a total of 1.95 gm. of stilbamidine and was reported as showing some evidence of suppression.[8]

This report concerns our experience with 2-hydroxystilbamidine in the treatment of seven patients with proved disseminated coccidioidomycosis.

* Received for publication November 29, 1954.

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Case Reports

Case 1. A 28 year old white Air Force Sergeant was well until 1951, when on routine examination a 1 by 1 cm. spherical nodule was noted in the right upper lobe of the lung in the second intercostal space. During several months of observation the patient remained asymptomatic except for a weight loss of 10 to 15 pounds; and the roentgenographic picture remained unchanged. While in the Air Force the patient had been stationed in Texas, Mississippi and Wyoming. A wedge resection of the pulmonary lesion, for a tentative diagnosis of tuberculoma, was performed in January, 1952. His postoperative course was stormy and was complicated by the development of a right loculated empyema.

The pathology report of the resected lesion showed a granulation tissue with foreign body giant cells. Subsequently, sinus tracts on the anterior chest wall continued to drain profusely and the patient lost an additional 30 pounds. Review of the sections of the pulmonary nodule showed a thick-walled, 1.5 cm. spherical lesion with a caseous center, tubercles and giant cells at the periphery, and thick-walled spherical bodies measuring 20 to 30 μ, suggesting a fibrocaseous pulmonary granuloma, probably coccidioidomycosis. In June, 1952, a right posterolateral thoracotomy was performed, with excision of seven draining sinus tracts and complete pulmonary decortication. Culture of the excised tissues revealed *Coccidioides immitis.* In July the patient began to complain of severe frontal headaches and photophobia, and developed stiff neck and increased fever. Examination of spinal fluid revealed pressure of 160 mm.; leukocytes, 2,000; total protein, 147 mg.; sugar, 52 mg.; chloride, 690 mg./100 c.c. Colloidal gold test read 1112222111. Culture was sterile.

The patient was transferred to the Mt. Sinai Hospital for 2-hydroxystilbamidine treatment of disseminated coccidioidomycosis with meningitis. Physical findings now revealed a temperature of 103.6° F., slight papilledema, stiff neck, positive Brudzinski's sign and tenderness over the right costal cage, where draining sinuses were noted. There were dullness and diminished breath sounds over the right anterior chest and right axilla, catheter drainage of the right thorax, a palpable spleen one and one-half fingerbreadths below the costal margin, clubbing of the fingers, hyperreflexia, ankle clonus and abnormal response to right plantar stimulation. Urinalysis and hemogram were normal. Erythrocyte sedimentation rate was 26 mm./hr. Total protein was 7.78 gm.; albumin, 3.55 gm.; globulin, 4.23 gm. per 100 c.c. Examination of spinal fluid confirmed previous findings, but, in addition, spherules of *Coccidioides immitis* were seen in wet preparations, and were subsequently confirmed by culture and guinea pig inoculation. X-ray of the chest showed a right pleural reaction, with loculated collections of fluid and pleural thickening. Electroencephalogram showed the presence of a mild diffuse encephalopathy.

The patient was treated with 2-hydroxystilbamidine, 250 mg. daily by intravenous infusion, from July 28, 1952, to November 5, 1952. At the end of the first month of treatment the spinal fluid showed a diminution of cell count to 205 leukocytes, sugar of 39 mg./100 c.c., chloride of 114 mEq./L, protein, 280 mg./100 c.c.; pressure remained elevated to 210 mm., and cultures remained positive. Following each injection of the drug the patient complained of nausea and vomiting. After a total dosage of 18 gm. of 2-hydroxystilbamidine, spinal findings remained unchanged but cultures were negative. There was considerable clinical improvement, with abatement of clinical signs of meningitis and only low grade fever. The draining sinuses of the chest wall had closed, and roentgenologically the pulmonary lesion had improved considerably. An additional 5 gm. of 2-hydroxystilbamidine were given, making a total of 23 gm., following which clinical improvement was sustained. Hepatic and renal function remained normal. Spinal fluid in November showed pressure of 160 mm., 85 lymphocytes, 2 polymorphonuclears, and persistence of low sugar and chloride and elevation of protein. Cultures were sterile.

At this time the patient complained of persistent nausea and vomiting, and daily headaches, and ran a temperature of 100° F. Weight was 111 pounds. No meningeal signs were noted. From December the patient showed slow but progressive improvement. Vomiting ceased, appetite improved, and there was a steady weight gain of 16 pounds. He had only occasional headaches, and his maximal temperature was 99.4° F. Spinal fluid examination in December showed a pressure of 170 mm., only 10 lymphocytes, sugar, 29 mg., and protein, 138 mg. per 100 c.c. Colloidal gold curve was now 000000222, and culture remained negative. In January, 1953, an exacerbation was characterized by fever, headache, vomiting, and a rise in spinal fluid cell count and protein. No localizing neurologic signs were observed, and in March serologic tests for coccidioidal infection (performed by Dr. Charles E. Smith) showed persistence of complement fixation in serum (1:64) and in spinal fluid (1:16). Without further therapy the patient again improved and was discharged. As of June, 1954, he had remained completely asymptomatic and had resumed his normal and even strenuous activities. As a matter of fact, he daily drives a heavy truck over a distance of about 100 miles. However, evidence of residual low grade infection persists. Spinal fluid obtained in May and June, 1954, respectively, still contained 160 cells per cubic millimeter, spinal fluid glucose remained lowered (36 mg./100 c.c.), and the protein elevation persisted (200 mg. %). No spherules could be found in the cerebrospinal fluid, and cultures have remained consistently negative. Complement fixation in the serum (May, 1954) persisted unchanged, but in the spinal fluid the titer had risen one serial dilution.

Case 2 (previously reported [11]). A 41 year old white male was stationed at Camp Iron Mountain in the Indio Desert in California from June to December, 1943. He was well until December, 1944, when, following trauma to his nose, he noted persistent nasal obstruction, crusting and pain. In May, 1946, he also developed painful swelling of the upper lip. In September, 1946, he was hospitalized for the first time, and biopsy and culture from both nostrils and lip were positive for *Coccidioides immitis*. From November, 1946, to January, 1951, he received several courses of x-ray therapy to the various regions of the mouth and nose.

On April 27, 1953, he was admitted to Hines Veterans Administration Hospital for the purpose of receiving 2-hydroxystilbamidine therapy. There was a 1 by 2 cm. perforation of the lower nasal septum, with surrounding dry, granulomatous nasal mucosa. The buccal mucosa was diffusely involved, with scarring and granulomatous lesions extending on to the hard and soft palates and into the tonsillar fossae. The tongue appeared thickened and scarred on its under surface and could not be protruded normally. A hemogram was normal. Liver and renal function tests were normal. Roentgenograms of the chest and spine were essentially normal. Biopsy and culture of the lesion of the tongue and soft palate were positive for *Coccidioides immitis*. Skin test with coccidioidin was positive in concentration of 1:100. Serologic tests for coccidioidal infection (performed by Dr. Charles E. Smith) showed complement fixation in serum at a titer of 1:128, and positive precipitin tests in undiluted serum.

On May 5, 1953 treatment with 2-hydroxystilbamidine was begun; 150 mg. dissolved in 200 c.c. of saline were given daily by intravenous injection. On May 20 he complained of severe pruritus following his injection of 2-hydroxystilbamidine, but medication was continued without recurrence of pruritus. On June 23 it was noted that he was somewhat drowsy, although he had no other complaints, and medication was discontinued for a three day period. By July 29 he complained of slight anorexia. By August 11 anorexia had become more marked and medication was stopped for three days. By August 20 he was becoming progressively less tolerant of the 2-hydroxystilbamidine, and complained of backache, headache, nausea and general malaise. After a three day rest period all symptoms subsided and medication was

started again. On August 29 he complained again of nausea and vomiting, and medication was again stopped. By the end of August he had received a total of 15,825 gm., or 0.28 gm./Kg., of 2-hydroxystilbamidine without subjective or objective improvement. The hemogram had been relatively constant throughout hospitalization. Urine was negative. Final sedimentation rate was 18 mm./hour. Liver and renal function tests and x-rays were essentially unchanged.

At his follow-up examination on January 29, 1954, the patient reported a five pound weight gain and less hoarseness. The left nasal lesion had healed and the ulcer on the dorsum of the tongue was smaller. On May 7 his weight had remained

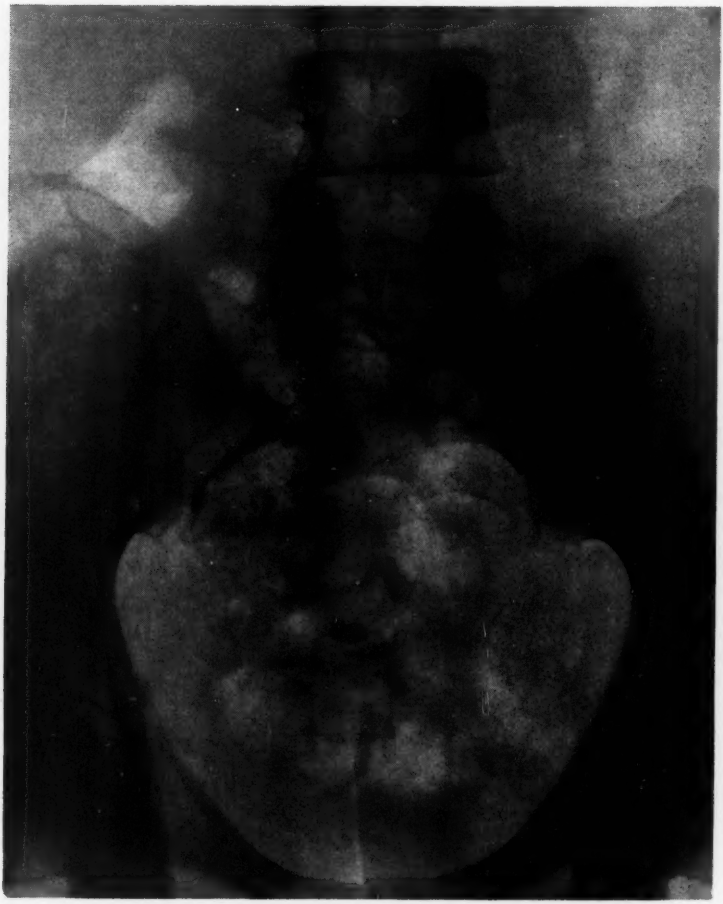

FIG. 1. *Case 3.* December 11, 1952. Large osteolytic lesion in ala of the superior part of left sacrum.

constant. Moderate hoarseness and dysphagia persisted, but he felt generally well. No ulceration was seen. The patient's condition was better than at any time since long before the initiation of 2-hydroxystilbamidine therapy.

Case 3. A 34 year old white male had been well until February, 1952, when he developed pain followed by swelling of the left side of the neck. He was in Phoenix, Arizona, from October, 1951, to April, 1952, and in Los Angeles, California, for four days in March, 1952. By August, 1952, he had lost 34 pounds in weight, and the mass in the neck had enlarged to the size of a golf ball. This abscess was incised and purulent material obtained, with subsequent persistent sinus drainage to the time of admission. Later in 1952 he developed pain across the buttocks and sacral region, for which he was given two x-ray treatments.

On December 17 1952, he was admitted to Hines Veterans Administration Hospital. He appeared chronically ill and poorly nourished. A small amount of yellow purulent material drained from a sinus on the left side of the neck. There were markedly tender fluctuant masses in both buttocks and sacral regions. Erythrocyte count was 3.84 million; leukocytes, 17,000, with 97% neutrophils; erythrocyte sedimentation rate, 29 mm./hour. Cultures of material draining from the cervical sinus and aspirated from the buttock abscesses were positive for *Coccidioides immitis.* Skin test with coccidioidin was negative in concentration of 1 : 100 but positive at 1 : 10. Serologic test for coccidioidal infection (performed by Dr. Charles E. Smith) showed complement fixation in serum at a titer of 1 : 32, and precipitin tests were positive in undiluted serum. Roentgenograms of the chest and cervical spine were negative. Pelvis films revealed a 3 cm. radiolucent area in the left ilium just adjacent to the upper margin of the left sacro-iliac joint (figure 1). Incisions were made on the lateral surface of each buttock and 750 c.c. of purulent material removed.

On December 24 he was given 50 mg. of stilbamidine. This was slowly increased to 150 mg., which he then received daily until he had had a total of 1.5 gm. of stilbamidine. No side effects and no subjective or objective changes were noted during this time. Lesions continued to drain, with the formation of chronic sinuses of the buttocks.

On March 12, 1953, treatment with 2-hydroxystilbamidine was begun, 225 mg. dissolved in 20 c.c. of 5% dextrose in water. Blood pressure before injection was 120/80 mm. of Hg. Before the injection was completed he complained of tingling of the scalp and entire body. He appeared flushed, and there was a very brief episode of nausea without vomiting. At the end of the injection his blood pressure was 80/60 mm. of Hg. In 10 minutes it rose to 90/62 and in one-half hour to 90–84 mm. of Hg, and he felt well. Subsequently the concentration was changed to 225 mg. of 2-hydroxystilbamidine diluted in 250 c.c. of saline intravenously. There was no immediate reaction. By March 18 he was mildly drowsy at times, complaining of mild anorexia and of occasional transient blurring of near vision. On April 9 his temperature rose to 101° F., on April 10 to 101.4° F. Physical examination revealed no specific changes. Hemogram, urine and chest x-rays were unchanged. On April 11 he was afebrile and there were no subsequent temperature elevations. On April 17 he complained of numbness over the bridge of the nose and forehead. On May 1 the concentration of 2-hydroxystilbamidine was changed to 150 mg. diluted in 200 c.c. of saline intravenously daily. On May 13 he complained of anorexia. On May 20 there was marked generalized pruritus with nausea and vomiting. By June 15 the numbness of the face had subsided and did not subsequently recur. By the end of August 1953, he had received a total of 18.125 gm., or 0.36 gm./Kg., of 2-hydroxystilbamidine. He had lost 10 pounds during the course of therapy. At this time roentgenograms of chest and spine were unchanged. Films of the pelvis revealed diminution in size of the previously described osteolytic lesion, with sclerosis of the bone adjacent to the remaining osteolytic lesion. On the last determination the hemo-

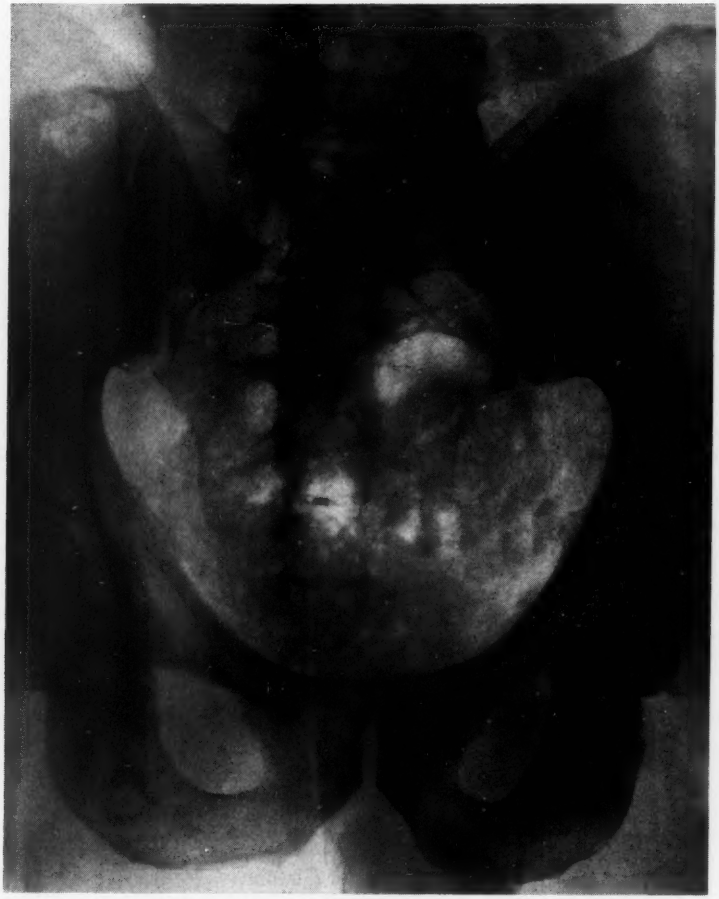

FIG. 2. *Case 3.* May 3, 1954. Osteolytic lesion in ala of left sacrum markedly improved. Healing with osteosclerosis.

gram was normal, erythrocyte sedimentation rate was 26 mm./hr., and the urine was negative. Cultures of material draining from the cervical and buttock sinuses were still positive for *Coccidioides immitis*. Liver and renal function tests were unchanged.

On reëxamination on May 6, 1954, it was noted that he had gained 20 pounds during the eight months following completion of 2-hydroxystilbamidine therapy. He was able to maintain full activity without undue fatigue. His appetite was greatly improved and he appeared alert and optimistic. His only complaint was the persistence of occasional transient discomfort in the cervical region. He felt that he had derived definite benefit from the 2-hydroxystilbamidine. Liver and renal func-

tions were essentially unchanged. The cervical and buttock sinuses did not appear changed, although drainage, previously thick and purulent, was now serosanguineous. Culture of this material for *Coccidioides immitis* was negative. Roentgenograms of the pelvis revealed the complete replacement of the previously described osteolytic lesion of the ilium by sclerosed bone (figure 2). Repeat serologic tests by Dr. C. E. Smith showed complement fixation in serum at a titer of 1:16. Dr. Smith felt this *might* represent a slight fall in titer.

Case 4 (previously reported [2]). A 31 year old Negro male had been well until May, 1949, when he developed a nonproductive, persistent cough. In June he noted a mass in the left lumbar region, with associated local pain and some elevation of temperature. He was regarded as a case of tuberculosis until culture of material aspirated from the lumbar mass was identified as *Coccidioides immitis*. The only source of contact elicited was that he had worked in the production of seat cushions in which hemp was used.

In January, 1950, he was admitted to Hines Veterans Administration Hospital. There was a large pleural effusion on the left and a 10 by 10 cm. soft fluctuant mass to the left of the first lumbar vertebra. Erythrocyte count was 3.2 million; hemoglobin, 9 gm.; total protein, 8.9 gm.; albumin, 3.5 gm.; globulin, 5.4 gm. per 100 c.c. Roentgenograms of the spine revealed a paravertebral abscess extending from D-6 to D-12, with involvement of cervical, dorsal and lumbar vertebrae. Smears and cultures of fluid aspirated from the chest and lumbar abscesses were positive for *Coccidioides immitis*. In March serologic tests for coccidioidal infection (performed by Dr. Charles E. Smith) showed complement fixation in serum at a titer of 1:64. Precipitin tests were negative, diluted and undiluted. He received supportive therapy and was discharged on September 19, 1951. At this time chest roentgenograms showed only small areas of irregular infiltration in both lower lung fields.

He was readmitted on February 3, 1953, with the complaint of productive cough of two months' duration. Three sputum cultures were positive for *Coccidioides immitis*. Roentgenograms of the spine showed no change from previous films. Serologic tests (performed by Dr. Charles E. Smith) revealed complement fixation in serum at a titer of 1:256. Precipitin tests were again negative. Skin test with coccidioidin was positive in a concentration of 1:10.

On March 12, 1953, 2-hydroxystilbamidine therapy was begun with 225 mg. in 20 c.c. of 5% dextrose in water intravenously. Before the injection was half-completed he complained of dizziness and tingling of the scalp and anterior chest; his blood pressure fell to 80/40 mm. of Hg. After 10 minutes his blood pressure rose to 90/60, and after one hour to 103/70 mm. of Hg. The concentration of 2-hydroxystilbamidine was then changed to 225 mg. diluted in 200 c.c. of saline and given slowly intravenously. There was no immediate reaction. On March 16 he complained of postprandial nausea and vomiting and low grade temperature elevation. On March 22 there were recurrence of nausea and a temperature rise to 103.6° F. There were no other complaints, and his physical examination was essentially unchanged except that a small left supraclavicular mass was noted for the first time. On March 23 his temperature again rose, to 104.2° F. The following day he was afebrile and had no subsequent temperature elevations. On April 6 anorexia and nausea again became marked, and 2-hydroxystilbamidine was stopped. It was started again on May 1, 150 mg. in 200 c.c. of saline intravenously. On June 16 definite fluctuation was noted in the left supraclavicular mass and the abscess was aspirated, yielding 40 c.c. of a thick, greenish white material. Smear and culture were positive for *Coccidioides immitis*.

By the end of August he had received 17.675 gm., or 0.35 gm./Kg., of 2-hydroxystilbamidine. At this time cervical spine films revealed further destructive changes.

Chest and lumbar spine films revealed no change from previous films. The supraclavicular mass previously described was still present and was increasing in size. Erythrocyte count was 3.8 million. Sedimentation rate was 29 mm./hr.; total protein, 7.6 gm.; albumin, 3.3 gm.; globulin, 4.4 gm. per 100 c.c. Other liver and renal functions were normal. The patient lost seven pounds during the course of treatment with 2-hydroxystilbamidine.

On reëxamination on May 6, 1954, he was found to have gained 20 pounds during the eight months following completion of 2-hydroxystilbamidine therapy. He was able to maintain full and even strenuous activity without undue fatigue but complained of low back discomfort following heavy work. His appetite was greatly improved and he felt he had derived definite benefit from the 2-hydroxystilbamidine. For the first time since the onset of illness he had had a return of sexual interest and capacity, and appeared alert and optimistic and definitely improved over his pretreatment appearance. The supraclavicular mass was no longer present, and only a slightly indurated area remained in its place. The remainder of the physical examination was essentially unchanged. Erythrocyte count was 4.3 million; erythrocyte sedimentation rate, 30 mm./hr.; total protein, 8.2 gm.; albumin, 3.5 gm.; globulin, 4.7 gm./100 c.c. Roentgenograms of the chest and entire spine were unchanged. Repeat complement fixation tests revealed no change in titer.

At this time it was felt that failure to obtain improvement in the spine or paravertebral abscess might in part be attributed to the lack of drainage of the abscess. Some form of drainage, possibly by aspiration, is therefore contemplated in the hope that further healing may occur.

Case 5. A nine year old white male child from Tucson, Arizona, had been well until the onset, in December, 1952, of fever, vomiting and biparietal headache. After four weeks of persistent headache and fever ranging to 102° F. he was treated successively with Terramycin, penicillin and streptomycin. In the fourth week of illness, rhinitis, cough and dullness over the right lower lobe were noted, and the child was regarded as having a patchy pneumonitis. X-ray of the chest was negative. In February, 1953, choreiform movements of the left arm were observed, fever ranged to 104° F., headache persisted and visual difficulty was noted. Studies at that time revealed normal optic discs, posturing, athetotic movements of the outstretched hands, and slight incoördination of the left upper extremity. Initial lumbar puncture revealed spinal fluid pressure of 165 mm.; sugar, 21 mg.; total protein, 114 mg. per 100 c.c.; 151 leukocytes per cubic millimeter, of which 67% were polymorphonuclear leukocytes and 33% were lymphocytes. Colloidal gold curve was 5554321000. Hemogram was normal. Erythrocyte sedimentation rate was 36 mm./hour. Coccidioidin skin test was negative, 1:100. Two subsequent examinations of spinal fluid revealed elevation of pressure to 265 mm., 295 leukocytes, of which 67% were lymphocytes, and persistence of marked lowering of sugar and elevation of protein. Cultures of spinal fluid were sterile. Serologic tests for coccidioidal infection (performed by Dr. Charles E. Smith) revealed complement fixation in serum at a titer of 1:32, in spinal fluid, 1:2, and positive precipitin test in serum 1:16, confirming the diagnosis of active coccidioidomycosis. Accordingly, the child was transferred to Columbus Hospital, Chicago, for therapy with 2-hydroxystilbamidine. Reëxamination revealed a thin, well developed child with striking pallor, fever of 104° F., widely dilated pupils, slight stiff neck, impairment of straight leg raising, dyssynergia of the upper left extremity, abnormal right plantar response, and inconstant Oppenheim's sign. Disc margins were indistinct nasally.

Roentgenograms of the chest, wrists and shoulders were negative. Hemoglobin was 10 gm.; erythrocytes, 3.55 million; leukocytes, 10,500, with 83% polymorphonuclear leukocytes. Blood total protein was 6.5 gm.; albumin, 3.9 gm.; globulin, 2.6 gm./100 c.c. Lumbar puncture revealed a pressure of 110 mm.; 240 cells (70%

lymphocytes, 30% polymorphonuclears); protein, 134 mg.; sugar, 22 mg./100 c.c.; chloride, 109 mEq./L. Colloidal curve was 5555321000. Hepatic and renal function were normal.

Initial observation revealed daily spikes in temperature to 103° F., headache and repeated episodes of vomiting. Shortly following his admission, early papilledema was noted. Treatment with 2-hydroxystilbamidine was instituted on February 27, 1953, in graduated dosage up to 90 mg./day, given intravenously in 20 c.c. of 5% dextrose in distilled water by slow direct injection. A transfusion of 200 c.c. of whole blood given on March 6 was followed by increase in well being and appetite. In the third week of treatment a transitory exacerbation of symptoms occurred, with stiff neck and progression of papilledema. At the end of the first month of treatment (totaling 3 gm.), apparent improvement was manifested by a feeling of well being, complete absence of symptoms and weight gain. The character of the temperature curve seemed changed: no further high spikes occurred, and the temperature daily fluctuated to 101° F. However, as treatment was continued, periodic transitory exacerbations occurred, accompanied by increased fever and papilledema, stiff neck, vomiting and elevation of cerebrospinal fluid pressure. These tended to be averted by frequent lumbar punctures, with reduction of cerebrospinal fluid pressure. In May, after a total dosage of 4.5 gm. of 2-hydroxystilbamidine, a severe exacerbation of symptoms was accompanied by an increase of cerebrospinal fluid pressure to 180 mm., increase of cell count to 700 (70% polymorphonuclears) and persistence of abnormal chemical findings. At this time, *Coccidioides immitis* was cultured from the spinal fluid and confirmed by Dr. C. E. Smith. The patient returned to Tucson, where the treatment was continued by the patient's physicians until June 18, 1953, to a total dosage of 7.7 gm. of 2-hydroxystilbamidine. Hepatic and renal function remained normal. There was persistence of anemia, fever and recurrent headache. Papilledema became chronic, and exacerbation of meningeal signs became more severe. Spinal fluid remained abnormal, with elevated pressure (285 mm.), pleocytosis (140 to 230 cells), persistently low sugar (8 to 30 mg.), protein of 120 to 170 mg./100 c.c., and persistence of abnormal colloidal gold curve. In July 1953, papilledema was severe; stiff neck and right Oppenheim's sign were present. Treatment with isonicotinic acid (100 mg. per day) was instituted, with no change in the clinical status. Serologic tests for coccidioidal infection (performed by Dr. Charles E. Smith) showed evidence of progression, with rise of serum complement fixation titer from its initial level of 1:32 to 1:128 in September. The serum precipitin test became negative, and spinal fluid complement fixation remained positive (1:8). Chronic papilledema and neurologic signs persisted. Because of increasing signs of block at the level of the brain stem a craniotomy for decompression was performed in January, 1954, but the child died.

Case 6. A 22 year old Negro farm laborer had been well until August, 1951, when he experienced an episode of right lateral chest pain, cough and expectoration of thick greenish sputum. At this time the patient had been in the San Joaquin Valley for 16 months, working as a tractor driver and cotton picker. Shortly after the episode of pleurisy, skin test with coccidioidin was positive. He subsequently complained of persistent fatigue and malaise. In January, 1952, tender masses appeared on the right chest and right arm, and in the right axillary and inguinal areas. The patient complained of weakness and marked night sweats. In April he was admitted to a local hospital for incision and drainage of abscesses on the chest wall and over the sternum, right shoulder and right forearm. Hemoglobin was 11.8 gm.; leukocytes, 17,600, with 88% polymorphonuclears. Serologic tests for coccidioidal infection revealed positive complement fixation at a titer of 1:32, and precipitin test was positive, 1:40. *Coccidioides immitis* was cultured from the abscess contents. X-ray of the chest revealed an infiltration in the right upper lobe and an erosion of

the right fifth and ninth ribs. In October, drainage of the sinuses having persisted, the patient was treated with a course of 14 intravenous injections of stilbamidine (total, 1,650 mg.); over a four week period the sinus drainage was noted to diminish and the patient was symptomatically improved. However, serum precipitin test was now positive in a titer of 1:100. Because of the persistence of draining sinuses, recurrent subcutaneous abscesses, fatigue, cough and a weight loss totaling 40 pounds, the patient presented himself for admission at Cook County Hospital * in March, 1953.

Pertinent physical findings included emaciation and multiple chronic draining sinuses surrounded by ulcerations measuring 0.5 to 5.0 cm. in diameter located over the upper sternum, right lateral chest wall and right inguinal areas. Several healed sinuses were noted over the right posterior thorax and the posterior aspect of the right forearm. The right supraclavicular fossa contained a 2 cm. fluctuant tender mass. The right costal cage was tender over the fifth rib in the anterior axillary line. The lungs were clear. A grade 1 systolic murmur was heard at the cardiac apex. Liver and spleen were not palpable.

Hemoglobin was 67%; erythrocytes, 3.66 million; leukocytes, 9,600, with 88% polymorphonuclear leukocytes. Erythrocyte sedimentation rate was 38 mm. per hour. Sternal marrow aspiration revealed toxic granulopoiesis and increase of eosinophils, plasma cells and monocytic cells. Total protein was 8.2 gm.; albumin, 4.2 gm.; globulin, 4.0 gm. per 100 c.c.; alkaline phosphatase, 7.4 Bodansky units; gamma globulin, 2.81 gm. per 100 c.c.

Coccidioidin skin test was positive in a dilution of 1:100. X-ray of the chest revealed an ill-defined density over the right lower lung field, prominence of the hilar regions, a radiolucency with fluid level in the soft tissue of the right mid thorax, a punched-out erosion of the superior margin of the anterior right fifth rib, and an irregular erosion of the inferior margin of the posterior right ninth rib. Hepatic and renal functions were normal.

Coccidioides immitis was repeatedly cultured from sputum and the draining skin sinuses. Serologic tests for coccidioidal infection (performed by Dr. Charles E. Smith) revealed a rise in titer of complement fixation to 1:256 and a fall in titer of precipitin test (positive 1:10). Spinal fluid showed negative serology; glucose, 62 mg.; protein, 26 mg. per 100 c.c., and sterile culture.

In vitro sensitivity studies revealed inhibition of growth of the coccidioides strain by 2-hydroxystilbamidine at a concentration of 50 mg. per cubic centimeter of medium, and by stilbamidine at a concentration of 100 mcg./c.c. Dr. Charles E. Smith demonstrated the diphasic character of the fungus by recovery of endosporulating spherules from lesions of peritoneum and lungs of an intraperitoneally inoculated mouse. The spherules grow out as fluffy white colonies.

The patient was treated with 2-hydroxystilbamidine from April 1, 1953, to July 24, in dosage of 150 to 225 mg. per day. The drug was given in fresh solution of 5% dextrose in distilled water. Initially the volume of solution was adjusted to 200 c.c., administered by rapid intravenous drip. Because of the development of severe nausea and vomiting, the dosage and volume were reduced to 150 mg. in 20 c.c., given by slow intravenous injection. The latter procedure in large part obviated the nausea which followed injections. A total dosage of 20 gm. of 2-hydroxystilbamidine was administered over a four month period. Hepatic and renal function remained normal. Early in the course of therapy the inguinal and presternal sinuses showed considerable diminution in size and drainage. However, healing was incomplete and cultures remained positive. The rib erosions persisted unchanged. Several new subcutaneous abscesses appeared from which the organism was recovered, and upon completion of treatment sputum cultures remained persistently

* Service of Dr. Francis L. Foran, Attending Physician, Cook County Hospital.

positive. Serial serum complement fixation tests showed rise in titer to 1:512. The patient's general condition slowly but progressively deteriorated during subsequent observation, and he died in April, 1954. At necropsy extensive osteomyelitis of the lumbar spine was found which led to bilateral psoas abscesses from which coccidioides was easily cultured. Pulmonary and lymph node granulomata were present from which pure cultures of *Candida albicans* were obtained. No other foci of coccidioidal granuloma were present. It would appear that terminally a moniliasis complicated the indolent, slowly progressive coccidioidomycosis.

Case 7. A 34 year old Negro male was admitted to Hines Veterans Administration Hospital on January 26, 1954. He complained of persistent, moderately productive cough of three months' duration, and of hoarseness and dysphagia of one month's duration. There had also been some wheezing on occasion, but no hemoptysis or dyspnea. He had lost 20 pounds in weight during the three months before admission. There was also a history of an ulcer on the dorsum of the nose and of a crusting lesion on the tip of the left index finger, present for about one year prior to the time of admission. He had been addicted to heroin for a short time, until about six months before admission. He had been in military service from 1942 to 1945, part of which time had been spent in the California desert.

On admission he appeared chronically ill, poorly nourished and older than his stated age. Blood pressure was 92/70 mm. of Hg; pulse, 80; temperature, 99° F. There was a 1.5 by 2 cm. crusted lesion with well defined edges on the dorsum of the nose. There was an area of indurated edema and crusting on the lateral border of the tip of the left index finger, with some involvement of the distal portion of the nail-bed. Examination of the larynx revealed considerable edema of the arytenoid and of the aryepiglottic folds. There was ulceration of the laryngeal surface of the epiglottis and, in addition, an ulcerative lesion in the inner arytenoid area which extended into the ventricles, where a fungating grayish white mass was seen. The false cords were edematous and were involved in the granulomatous process. There appeared to be a subglottic extension of the lesion.

Admission hemogram and serology were negative. Initial urinalysis revealed a faint trace of albumin. Liver and renal functions and electrolyte levels were normal except that the total protein was 8.8 gm., albumin 2.5 gm. and globulin 6.3 gm./100 c.c. Chest x-ray was normal. Laminagrams of the larynx revealed bilateral fusiform masses in the larynx which occluded the central passages. X-rays of the nose did not show evidence of bone erosion or destruction. X-ray of the left index finger revealed a small localized area of bone erosion along the lateral border of the distal portion of the distal phalanx.

On February 3, 1954 a prophylactic tracheotomy was performed at the level of the fifth ring. A grayish lesion was seen to line the trachea at this level. Biopsy and culture of this lesion were reported positive for *Coccidioides immitis.* Subsequent biopsies of the lesions of the nose and left index finger were also positive for *Coccidioides immitis.*

On February 12 therapy was begun with daily intravenous infusions of 150 mg. of 2-hydroxystilbamidine diluted in 200 c.c. of normal saline. By the time the patient had received a total of 10 gm. he began to complain of anorexia and some nausea. He also occasionally complained of a sensation of burning and itching "from the neck down" following administration of medication. These complaints, however, have been intermittent and have not at any time been sufficiently severe to require a rest period from the medication. Serologic tests for coccidioidal infection were not done until the beginning of June 1954. Complement fixations at this time were positive in serum at a titer of 1:128; precipitin tests were negative.

By the end of June he had received a total of 20 gm., or 0.4 gm./Kg. of 2-hydroxystilbamidine. He had lost 11 pounds in weight since the time of admission.

The nasal lesion appeared completely healed. The finger lesion appeared almost healed, with no further crusting or ulcerations. X-rays of the finger, however, revealed no evidence of healing. X-rays of larynx, nose and chest were essentially unchanged. Sedimentation rate was 16 mm./hr. Serum albumin was 3.1 gm.; globulin, 5.7 gm./100 c.c. Cough has diminished, and the laryngeal lesion shows less edema but is otherwise unchanged. The tracheotomy tube has been removed. Appetite is improving.

Comments

The low toxicity of 2-hydroxystilbamidine was the reason why this compound was selected as a possibly effective agent in disseminated coccidioidomycosis. It may be noted that the in vitro sensitivity of coccidioides to stilbamidine and 2-hydroxystilbamidine is comparable to the sensitivity of relatively resistant strains of *Blastomyces dermatitidis*.[9, 23] It was thought that if sufficient total dosage could be given the disease might be arrested or cured.

A review of the course, physical findings and laboratory data in all of the above cases reveals no evidence of curative effect on disseminated coccidioidomycosis. However, it appears possible that, in at least five of the seven patients, 2-hydroxystilbamidine therapy was followed by more or less marked suppression of the disease, manifested by progressive subsidence of complaints, and frequently by weight gain and resumption of normal activities. This was most impressive in case 1, in whom a remarkable remission of the progressive coccidioidal meningitis coincided with high dosage therapy with 2-hydroxystilbamidine, totaling 23 gm. However, in the five patients who appeared clinically improved evidence of persistent low grade infection remains, and serologic improvement during and after the treatment is discouragingly small. The impression was obtained that after completion of the treatment the acute infection with *Coccidioides immitis* had been so markedly reduced in activity that a condition nowadays commonly designated as commensalism had resulted. It seems likely that even with the large total dosage of 2-hydroxystilbamidine administered, tissue concentrations were nevertheless inadequate. The gastrointestinal and general symptoms in our patients were such that the achievement of significantly higher concentrations of this drug does not appear to be attainable.

Possibly some of the improvement in these patients may be attributed to the relief of nausea following discontinuation of 2-hydroxystilbamidine therapy, and possibly some may be attributed to the patient's attitude of optimism associated with the hope of cure following the long course of therapy. These factors, however, cannot alone explain the considerable clinical improvement in these patients, and it is felt that at least partial suppression of their disease may be attributed to 2-hydroxystilbamidine therapy. It is of some interest that when clinical improvement occurred, it usually appeared only two to six months following cessation of treatment. This may be understandable in terms of the depository character of the drug, which may permit prolonged action following cessation of treatment. Even

two years after termination of 2-hydroxystilbamidine, small amounts of this drug could be found in adrenals and liver.[24] The doses administered in the latter cases were much smaller than those given to the patients with coccidioidomycosis reported here.

It may be emphasized that, despite total dosage of 23 gm., 7.7 gm. (in a nine year old child), 20 gm., 17 gm., 15.83 gm. and 18.13 gm., respectively, ranging from 0.30 to 0.4 gm. per kilogram, no evidence of renal or hepatic toxicity attributable to the drug was noted. This is consistent with the experience that properly administered (in fresh solution protected from light), 2-hydroxystilbamidine may be given in large doses with no serious toxicity.[21, 22, 25]

In case 3, facial numbness appeared four months after a course of 1.5 gm. of stilbamidine but subsided during the subsequent administration of 2-hydroxystilbamidine.[1, 4, 18] Other instances of delayed appearance of a mild neuropathy have been observed in patients treated with only several hundred milligrams of stilbamidine and subsequent full therapeutic doses of the 2-hydroxy derivative. It seems safe to attribute such incidents to the antecedent stilbamidine therapy.

As with stilbamidine, immediate reactions may occur during intravenous injection of the drug. A nitritoid reaction was noted in some cases when high concentrations of 2-hydroxystilbamidine were administered intravenously.[10, 27] These were easily avoided by decreasing the concentration per unit time of injection, either by increasing the dilution or by slowing the injection.

Formication noted with the use of stilbamidine [10] was also noted in the current series treated with 2-hydroxystilbamidine, again dependent on rapidity of injection.

Nausea and vomiting appeared to be directly attributable to 2-hydroxystilbamidine and became progressively more annoying with increasing total dosage. Shorter courses and longer rest periods were required later in the course of therapy. After receiving 10 to 14 gm. of 2-hydroxystilbamidine patients complained of malaise, weakness, headache and muscle aching, in addition to nausea and vomiting, all of which subsided with rest periods and recurred with further treatment. Altering the concentration of the drug or the speed of injection did not appear to alter the side effects greatly. However, in one instance slow direct intravenous syringe injection appeared to diminish nausea following injection. Precautions taken to avoid toxicity of the drug are all related to its instability in solution and sensitivity to ultraviolet light. The drug was stored in powder form and was not put into solution until immediately before use. The drug, both in substance and in solution, was protected against light, and undue exposure of the patient to sunlight was avoided.

It is perhaps noteworthy that side effects were most marked in the patients with severe chronic illness and constitutional complaints prior to

therapy. Only case 2 did not appear chronically ill, but was well nourished and without systemic complaints at the onset of therapy. Nausea in this patient was only a minor problem.

It may also be of some interest that in the treatment of blastomycosis with large doses of stilbamidine and 2-hydroxystilbamidine,[23, 25] little or no nausea was encountered.

For the time being, it may be said that while 2-hydroxystilbamidine appears to have no curative effect on disseminated coccidioidomycosis, it is nevertheless not without value. Further use of 2-hydroxystilbamidine in the treatment of disseminated coccidioidomycosis, with long follow-up and in a larger number of patients, appears to be indicated before its place in the treatment of this disease can be properly evaluated. Search for other stilbamidine derivatives with more specific action upon *Coccidioides immitis* continues.

Summary

1. Seven patients with disseminated coccidioidomycosis were treated with 2-hydroxystilbamidine in dosage of 8 to 23 gm.

2. In five patients there was evidence of a suppressive effect on the progression of the disease, with evidence of persistent low grade infection. Two patients died.

3. Despite the high dosage administered no instance of toxicity occurred. Gastrointestinal side-effects were troublesome but subsided on withdrawal of the drug.

Acknowledgments

This investigation was supported in part by a research grant (E-483) from the National Microbiological Institute of the National Institutes of Health, Public Health Service, and in part by a grant from the Dr. Leonard H. and Louis D. Weissman Medical Research Foundation. The 2-hydroxystilbamidine used was generously supplied by the Merrell Company.

All of the serologic tests for coccidioidal infection, as well as final identification of the organism, and drug sensitivity studies, were generously performed by Dr. Charles E. Smith, University of California, School of Public Health.

Summario in Interlingua

Disseminate coccidioidomycosis in le forma progressive o meningitic es invariabilemente mortal. Recente incoragiante resultatos obtenite per medio de stilbamidina e su derivatos in le tractamento de altere disseminate morbos mycotic, specialmente de blastomycosis, ha inspirate le investigation hic reportate del efficacia de iste gruppo de compositos in casos de coccidioidomycosis.

Stilbamidina in alte concentrationes inhibi in vitro le crescentia de *Coccidioides immitis*, sed le frequente occurrentia de neuropathia trigeminal post le administration de large quantitates de stilbamidina limita le dosage total que pote esser prescribite. Su derivato, 2-hydroxystilbamidina, es equalmente efficace in le tractamento de blastomycosis. Illo es non-toxic e assi pote esser administrate in plus grande doses. Isto rende possibile le attingimento de histoconcentrationes del droga sufficiente pro influentiar le curso del infection coccidioidic.

Un gruppo de 7 patientes con progressive coccidioidomycosis disseminate de etates de inter 9 e 41 annos, esseva tractate con 2-hydroxystilbamidina. Duo habeva chronic

meningitis; le altere 5 habeva involvimento del pulmone, del ossos, del nodos lymphatic, del superficies mucose, e del pelle. Le droga esseva administrate intravenosemente in doses de inter 150 e 225 mg per die, tanto per injection directe como etiam per infusion rapide. Le dosages total variava ab 7,7 a 23,0 g, i.e. ab 0,30 a 0,40 g per kg de peso corporee. Un reaction nitritoide que occurreva durante le injection esseva facilemente eliminate per reducer le concentration del droga in le injectiones individual. Durante le tractamento omne le patientes experientiava sever attaccos de nausea e vomito de grados de severitate accrescente con le dosage total. Le nausea inducite per le droga esseva le plus sever in ille patientes qui habeva habite serie symptomas constitutional e debilitate ante le comenciamento del curso de therapia. In despecto del alte dosage nulle altere manifestationes toxic causate per le droga esseva observate. Duo patientes moriva. Uno de illes esseva inter le casos con chronic meningitis. Cinque del patientes esseva considerate como meliorate in tanto que le cessation del therapia esseva sequite post periodos de inter 2 e 6 menses per un progressive reduction del symptomas, per augmento de peso corporee, e per le resumption de activitates normal. Omne iste 5 patientes habeva persistente signos de infection a grado minor, e le essayo a fixation del complemento seral remaneva positive. In un patiente un frappante melioration de un lesion ossee esseva observate roentgenologicamente: un lesion osteolytic del ilio con un diametro de 3 cm habeva essite completemente reimplaciate per osso nove. Il pare que le tractamento a 2-hydroxystilbamidina ha alicun influentia suppressive—ben que non curative—super le infection coccidioidic.

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THE CHEMOPROPHYLAXIS OF INFECTION *

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The effectiveness of the antimicrobial agents in eliminating certain organisms and in curing the diseases produced by them has led to their use for the prevention of specific infectious processes, or of infection in general. The results obtained when antibiotics have been employed for this purpose have been quite variable. In some instances chemoprophylaxis has been eminently successful, in others it has failed completely, while in still others no conclusion can be reached because of the inadequacies of the available data.

Chemoprophylaxis has been used primarily for four purposes: (1) to protect healthy individuals, either singly or in groups, against invasion by specific microörganisms; (2) to prevent secondary bacterial infection in people acutely ill with diseases for which the antimicrobial agents are not effective; (3) to reduce the risk of infection in patients with various types of chronic illness; and (4) to inhibit the spread of disease from areas of localized infection, or to prevent infection in general, in persons who have been subjected to accidental or surgical trauma. The degree of success has varied with the purpose for which prophylaxis has been applied; it has been highest when the prevention of specific infections has been attempted, and lowest when protection against infection in general has been its aim. In many instances, prophylactic measures have been applied only to single individuals; in others, they have been used for large groups. In many cases, chemoprophylaxis, whether effective or not, has resulted in no untoward reactions; in some, it has converted a benign, self-limited disease into a serious or even life-threatening one.

Chemoprophylaxis in some infectious diseases is based on studies which have confirmed its usefulness. In others, however, it has been predicated on theoretic considerations or unproved clinical impressions and has not been subjected to adequate and controlled investigation. Since there are confusion and lack of agreement concerning areas of use and effectiveness of chemoprophylaxis, it is the purpose of this paper to review briefly the conditions in which this treatment has been employed and to point out those in which it appears to be of proved value, of questionable merit, or useless. Since chemoprophylaxis is not a procedure which is entirely safe, a few remarks will be made concerning the dangers involved.

* From the Symposium on Infection, presented at the Thirty-sixth Annual Session of the American College of Physicians, Philadelphia, Pennsylvania, April 29, 1955.

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Chemoprophylaxis In Healthy Individuals

Chemoprophylaxis is most commonly employed in healthy individuals to prevent invasion by specific bacteria. It has been given either to single patients, to families, or to large groups of people, some of whom had not yet had contact with an organism and others of whom were already harboring it as asymptomatic carriers. This type of prophylaxis has, as a rule, been most successful in protecting against infection by four agents—the beta-hemolytic streptococcus, the gonococcus, the meningococcus and the dysentery bacilli.

The administration of chemotherapeutic agents to individuals exposed to invasion by the beta-hemolytic streptococcus affords a predictable and high order of protection. One of the factors which limit the use of the sulfonamides is the presence of a variable number of resistant strains of the organism. Although several antibiotics have been used for this purpose, penicillin appears to be the drug of choice.[4, 30] The oral ingestion of 200,000 units of buffered benzyl penicillin G twice a day for five days, or a single injection of 600,000 units of procaine penicillin with aluminum monostearate, has been found to be effective. Benzethacil (Bicillin), given either by mouth or by a single intramuscular instillation of 600,000 units, has also been said to produce good results. If penicillin cannot be given, one of the tetracycline compounds or erythromycin may be employed. In large population groups in which streptococcal infection appears, there are usually a number of asymptomatic carriers. Since a larger quantity of antibiotic and a longer period of therapy are required for the elimination of bacteria than to prevent their initial implantation, the prophylaxis of the carrier state necessitates using the same dose of drug and duration of treatment as in established streptococcosis. The administration of 250,000 units of benzyl penicillin G orally twice daily for 10 days to all contacts may abort promptly an epidemic of streptococcal disease and reduce markedly the carrier rate.

Penicillin is a highly effective prophylactic agent in healthy individuals exposed to gonorrhea. A single oral dose of 250,000 units given immediately after contact has been demonstrated by Eagle et al.[7] to reduce markedly the incidence of this disease (one questionable case in 141 treated men, as contrasted to an incidence of 508 cases per 1,000 in those receiving a placebo). The rôle of such prophylaxis in suppressing manifestations of syphilis without completely eliminating the infection remains to be investigated. The instillation of penicillin solution into the conjunctival sac protects the newborn child against gonorrheal ophthalmia.[10]

The sulfonamides are the most effective agents for the prevention of bacillary dysentery.[2, 8] The rapidly absorbable drugs such as sulfadiazine or sulfamerazine are usually better than sulfaguanidine, sulfathalidine or sulfasuxidine. One of the factors which occasionally limit the use of the sulfonamides is the presence of drug-resistant strains of dysentery bacilli. The dose of sulfadiazine recommended for prophylaxis of bacillary dysentery

is 0.5 gm. twice a day for five days. In outbreaks due to sulfonamide-insensitive organisms, chloramphenicol, chlortetracycline (Aureomycin) or other tetracycline compounds may be employed.

The availability of potent antimicrobial agents has made the prevention of all degrees of spread of meningococcal infection a relatively simple matter.[18, 24] The meningococcus is highly sensitive to sulfadiazine; although resistance of a rare strain of the organisms to this drug has been suspected, it has not been proved. A completely effective dose of sulfadiazine is 1 to 2 gm. at one time, or 0.5 gm. twice a day for two days.

Chemoprophylaxis In Acutely Ill Individuals

The antimicrobial agents have been used extensively for the prevention of bacterial invasion in individuals taken suddenly ill with disorders in which these drugs have no therapeutic effect. The primary diseases in which such chemoprophylaxis has been employed are of two types: (1) those due to various viruses, and (2) those which are noninfectious in origin.

One of the most common prophylactic uses of the antibiotics is in undefined viral disease of the upper respiratory tract. Attempts to prevent secondary infections following the "common cold," while most desirable, have not proved very successful. Although it has been the impression of some clinicians that benefit was derived from such prophylaxis, this is not based on studies of large groups of patients with an adequate number of untreated controls. Depending on the antimicrobial agent used, certain pathogenic bacteria may be prevented from producing disease in the person with a viral respiratory infection. However, regardless of the prophylactic program employed, invasion by all organisms cannot be eliminated. For this reason the etiology of the complications may be altered by chemoprophylaxis, but their incidence may be very little if at all changed. There is considerable question whether prophylaxis should be given in "primary atypical pneumonia" or some of the other undefined viral pneumonitides, since secondary bacterial infection in untreated cases is uncommon. In viral influenza, the risk of superimposed bacterial disease is greater than in the undefined viral pneumonias, and chemoprophylaxis may therefore have more justification. It is important to emphasize, however, that complicating infections by bacteria cannot be completely avoided and that, when they occur, they may be very serious and caused by *Proteus* or *Staphylococcus aureus,* or other organisms relatively difficult to eliminate. The lack of success of prophylaxis in most of the viral respiratory diseases has had little or no influence on its widespread use for this purpose.

Antibiotics have often been administered in the so-called "childhood diseases" to prevent secondary bacterial infection. Both penicillin and chlortetracycline (Aureomycin) have been reported to reduce remarkably the number of complications in measles.[14, 15] A recent study of this disease in our clinic has not, however, indicated any benefit from the administration

of chemotherapeutic agents during the preëruptive or eruptive phase.[31] In fact, the data have suggested that the incidence of secondary bacterial infections may be higher in patients given an antibiotic than in those not treated. Of 428 cases of rubeola entering the hospital, 130 had received prophylactic antimicrobial agents prior to admission. Secondary bacterial infections were present in 30.4% of this group. In 298 cases given no antibiotic while at home, the incidence of proved superimposed bacterial disease was approximately half as great (14.9%). The organisms most commonly responsible for complications in the untreated patients were the pneumococcus, the beta-hemolytic streptococcus, *Staphylococcus aureus,* and *Hemophilus influenzae,* each being found in about 20%. Fifty-eight per cent of the infections occurring during prophylaxis, on the other hand, were due to *H. influenzae; Staph. aureus* was present in 11%, and the pneumococcus and beta-hemolytic streptococcus in 3% and 5%, respectively. The type of complicating disease present was also influenced by chemoprophylaxis. Thus, in treated patients pneumonia occurred in 78%, while in untreated ones it occurred in 57%. Of 350 cases of untreated measles entering the hospital with no evidence of superimposed infection and given no therapy after admission, 4.6% developed secondary bacterial disease.

Failure of antimicrobial agents to protect against bacterial invasion in "respiratory" poliomyelitis has also been observed in our clinic.[32] In 165 patients with bulbar involvement or paralysis of respiratory muscles who received no antibiotics, the incidence of secondary infections was 16%. In 63 persons with the same type of disease who were given chemoprophylaxis, bacterial complications occurred in 53%, approximately three and one-half times as many as were observed when no drugs were given. Although the more seriously ill cases were the ones most often treated—and this may have accounted, in part, for the larger number of superimposed infections in this group—the fact remains that prophylaxis failed to protect those who were in the greatest need of protection. Of importance is the fact that pneumonia, the complication most feared in "respiratory" poliomyelitis, occurred in 22% of the patients given chemoprophylaxis and in only 6% of those who received no antibacterial agents. Of significance also is the etiology of the pulmonary infections: in the treated individuals, the most common causative organisms were *Pseudomonas pyocyanea,* penicillin-resistant *Staph. aureus* and *H. influenzae,* while in the untreated ones the bacteria found most often were the pneumococcus and the beta-hemolytic streptococcus.

Our experience in the prevention of superimposed bacterial disease in pertussis has been very disappointing.[33] In 139 patients given no specific therapy, superinfections occurred in 21.4%; in 55 receiving chloramphenicol or chlortetracycline (Aureomycin), the incidence of complications was not reduced. In addition, the organisms responsible for secondary infection in the treated children frequently were *Proteus, Ps. pyocyanea* and members

of the colon-aerogenes group, many strains of which are relatively insensitive to antibacterial drugs.

Although antimicrobial agents of various types have been used in mumps, chickenpox and infectious mononucleosis, both as therapy for the primary disease and as prophylaxis against bacterial infection, there is no evidence that they produce a beneficial effect. A recent study of varicella in our clinic has revealed no reduction in the incidence of superimposed bacterial disease by chemoprophylaxis.

It is common practice in many hospitals to administer antibiotic agents to patients with heart failure, coma due to various causes, cerebrovascular accidents or shock for the purpose of preventing bacterial infections. Despite the wide use of such prophylaxis and the general impression that it is effective, little or no conclusive evidence has been obtained from controlled observation to substantiate its usefulness. Since individuals with these conditions are quite susceptible to bacterial invasion, they are exposed to the risk of superinfection even if they receive antibiotics. This has indeed been our experience, and it illustrates the impossibility of completely preventing infection, despite the use of potent drugs given alone or in various combinations.

The necessity to catheterize the urinary bladder usually arises as an acute situation. Although single catheterizations are attended by a certain risk of infection of the lower urinary tract, the presence of an indwelling tube is almost certain to result in bacterial invasion of the bladder or kidneys, or both. The sulfonamides, usually in a dose of 2 gm. a day, have been used for a long time for prophylaxis in this situation. The results with these drugs have been variable. That their use in the usual quantities is often without benefit, in the face of constant catheter drainage, has been brought to our attention in poliomyelitis patients, 20% of whom have developed infection of the urinary tract after insertion of a Foley catheter, despite the administration of sulfonamides. The use of other antibiotic agents has not significantly altered the situation. On the basis of this experience, two other approaches to this problem have suggested themselves. The first is tidal drainage; this definitely reduces the risk of infection. The other involves increasing the dose of the prophylactic agent to full therapeutic levels for at least one week after removal of the catheter because the quantities of drug used for prophylaxis frequently do not prevent bacteria from being present in appreciable numbers, despite absence of active infection. With cessation of treatment, the organisms often multiply and invade the tissues. The administration of large doses of a chemotherapeutic agent may eliminate the bacteria before they produce disease. It is of great importance to emphasize the necessity of encouraging a patient to void before catheterization is resorted to. In many instances, urinary retention is acute in onset and short in duration and, with patience and proper management, the insertion of a tube into the bladder may not be necessary. One of the

most effective ways to prevent urinary tract infection is to avoid, wherever possible, the use of the catheter.

On the whole, chemoprophylaxis in patients with acute diseases for which antimicrobial agents are not effective is not very successful. Since, in addition, there is always the risk of superinfection and other reactions, some of which may be serious, the use of antibiotics to prevent secondary infections in the conditions just discussed may not be justifiable, except in unusual circumstances.

Chemoprophylaxis In Chronic Disease

While not all individuals who have had rheumatic fever have residual valvular defects, their susceptibility to new episodes of the acute rheumatic state and the risk of cardiac damage make it imperative that everyone who has recovered from this disease be protected against infection by the beta-hemolytic streptococcus, which is responsible in most instances for recurrences. The two agents which have been used most extensively for the prevention of rheumatic fever are sulfadiazine and penicillin. The administration of 1 gm. of sulfadiazine per day has been found to reduce the recurrence rate by 85%; the incidence of reactions with this drug is low (0.1% mild and 0.01% severe).[1, 6, 19, 27] Both parenteral and oral preparations of penicillin have been employed for the same purpose. Very satisfactory results have been noted with this antibiotic; in some groups, recurrence of rheumatic fever has been entirely eliminated.[16, 17] One of the problems which still remain to be resolved in the use of penicillin is establishment of the optimal dose. Quantities ranging from 100,000 units twice a day to 200,000 units three times a day have been given by mouth, with success. Most recently, it has been reported that a single intramuscular injection of 600,000 units of Benzethacil (Bicillin) prevents rheumatic fever recurrences completely.[5, 28] Regardless of the nature of the antimicrobial agent employed, prophylaxis must be given daily throughout the year. In adults it is advisable to continue treatment for a minimum of five years, while in children the drug should be administered prophylactically at least through puberty. It has recently been suggested that prophylaxis be continued throughout the entire life of the patient.[34]

It has been estimated that about 25% of cases of subacute bacterial endocarditis follow dental extraction. This observation and the fact that transient bacteremia occurs in from 20 to 60% of persons who have teeth removed have emphasized the importance of chemoprophylaxis in patients with acquired or congenital heart disease. The sulfonamides have been used for this purpose, but they are not the drug of choice. Penicillin is the agent which has been employed most often, and it appears to be very effective in preventing infection of the cardiac valves, although bacteremia may not always be eliminated.[11, 12] There is at present no agreement as to optimal dosage and time of administration of penicillin. In some instances a single

dose of procaine penicillin has been given two to three hours before dental extraction. In others, crystalline penicillin G has been injected in large doses for varying periods of time prior to and after removal of teeth. Most recently, Aureomycin has been reported to be effective.[26]

Patients with chronic bronchitis, emphysema and bronchiectasis are highly susceptible to superimposed bacterial infections. McVay and Sprunt [21] have reported that the administration of 0.5 gm. of chloramphenicol daily to individuals with these disorders resulted in a reduction in respiratory infections of 50%. Also apparent were greater weight gain, improved appetite and "increase of energy and zest for life." The same investigators also made an attempt to reduce the number of infections in diabetes mellitus.[22] They gave 94 patients with this disease 0.5 gm. of chlortetracycline (Aureomycin) daily for an average of 19 months, while 95 others received a placebo; fewer respiratory and urinary tract infections were observed in the treated cases.

Children with cystic fibrosis of the pancreas (mucoviscidosis) are particularly susceptible to infections of the lung, especially by *Staph. aureus.* For this reason, Shwachman [28] has used chlortetracycline (Aureomycin) as prophylaxis in this disease. Although staphylococcus can often be cultured from the respiratory tract of these patients while they are receiving this drug, the risk of repeated episodes of pneumonia is sharply reduced and life is prolonged and made much more comfortable.

It is apparent from the data which have been presented that chemoprophylaxis of chronic illness yields variable results. The use of antibiotic agents to prevent recurrences of rheumatic fever is highly successful. Whether a significant degree of reduction in the incidence of infection in chronic lung disease or diabetes mellitus can be accomplished remains to be proved.

Chemoprophylaxis of Surgical or Accidental Trauma

One of the most common areas of use of chemoprophylactic agents has been in elective surgery. The purpose of this has been to prevent postoperative pulmonary and other infections. Although the general impression has been that the administration of antimicrobial agents results in a reduction in the incidence of postoperative infectious complications, a recent report by McKittrick and Wheelock [20] has emphasized the failure of prophylaxis in such cases. In a number of patients subjected to elective abdominal surgery and given antibiotic agents, they found no significant difference in the frequency of postoperative sequelae when compared to a group in which no chemotherapy was used. Howe [13] has recorded a recent increase in the rate of infection of clean wounds after operation, despite the prophylactic use of antibiotics, and has pointed out that, in his patients, this was due primarily to invasion by penicillin-resistant *Staph. aureus,* which had probably been acquired from medical and other attendants. There is no

evidence that the number of postoperative pulmonary complications is decreased by chemoprophylaxis.

Antibiotics in various combinations have been used extensively for preparation of the bowel for surgery.[3, 25] The agents which have been employed most widely for this purpose have been the so-called "broad spectrum" antibiotics. Although the number of organisms in the intestine may be markedly reduced, complete sterilization has rarely, if ever, been accomplished. While it may appear that the incidence of postoperative peritonitis has been decreased by this procedure, the fact remains that adequate controlled investigations of this problem have not been carried out. Furthermore, the administration of large quantities or mixtures of antibiotics is not without danger; pseudomembranous colitis or acute staphylococcal enteritis (either of which may be fatal) occasionally appears during the course of antibiotic preparation of the intestine for surgery.

Surgical treatment of infected areas, such as the tuberculous lung,[28] localized abscesses, bronchiectasis and others, is an indication for the use of chemoprophylaxis prior to and after operation. In this type of surgery the administration of antimicrobial agents appears justified even in the face of the risks which may be involved. The type of drug employed must be determined by the location and etiology of the infection. In accidental wounds or burns, chemoprophylaxis has not been as successful as might have been expected. In our experience the administration of penicillin to patients with burns has not prevented infection by staphylococci resistant to this agent, or by gram-negative bacteria difficult to eradicate with antimicrobial drugs. Infection is not completely prevented even when combinations of antibiotics are given; in these instances, the organisms involved are frequently *Proteus* or *Pseudomonas*. The ineffectiveness of sulfonamide powder in preventing infection in wounds is well known.

In obstetrical practice, patients with prolonged and difficult labor are susceptible to puerperal infection, and the use of an antibiotic to prevent this complication may be justified. On the other hand, the general application of chemoprophylaxis to all women after completion of labor requires substantiation of its necessity. Careful studies, including an adequate number of untreated controls to prove the effectiveness of this type of prophylaxis, remain to be carried out.

Dangers of Chemoprophylaxis

No discussion of chemoprophylaxis would be complete without at least mentioning the difficulties which may be encountered. It is important to point out that the same untoward effects which occur when antibiotic agents are used for therapeutic purposes[9] are observed when patients who have no active infection are given these drugs. Thus, allergic episodes varying in severity from mild skin rashes to fatal attacks of acute anaphylaxis, a variety of reactions due to the irritating and toxic properties of the anti-

microbial agents, disturbances in metabolism and serious superinfections have occurred in individuals who have been given antibiotics for the prevention of bacterial invasion. The risk of the development of reactions and the difficulties which they involve must always be taken into consideration in planning a program of chemoprophylaxis. In instances where the use of antibiotic agents for protection against infection is of proved value, taking this risk is completely justified. In cases where the effectiveness of prophylaxis is questionable, the situation must be carefully scrutinized before treatment is started and the benefits to be derived must be weighed against the possible dangers. When there is no evidence that chemoprophylaxis will be effective, it should not be given. It has been pointed out that the use of any powerful therapeutic substance is accompanied by a calculated risk. This is worth taking if benefit is derived from treatment; it is unjustifiable if it is clear that no good can be accomplished.

Summary and Comment

In summary, it should be pointed out that the chemoprophylaxis of infection requires more intensive and controlled study than it has received. It is obvious that some serious diseases can be completely prevented by the proper administration of antibacterial agents. The degree of success appears to be highest when the prophylactic measures are aimed at specific microörganisms. On the other hand, there are a number of conditions in which the use of antibiotics for protection against bacterial invasion is not justified, either because this type of complication is very uncommon or because there is proof that the desired result will not be produced. It is striking that the clinical areas in which prophylaxis has been applied most widely are those in which its use has been based mainly on clinical impression rather than on fact derived from careful study. It is in some of these situations that more investigation is necessary before the true value of the chemoprophylactic procedures which have been employed can be determined. There is no doubt that the availability of the antibacterial compounds has already contributed greatly *and can contribute even more* to the effectiveness of preventive medicine. For this reason, it is imperative that this field of application of the antimicrobial drugs be given the same degree of attention and carefully controlled study that the therapeutic use of these agents has received.

Summario in Interlingua

Chimoprophylaxis anti-infectiose per medio de agentes antibacterial se ha usate principalmente con un del sequente quatro objectivos: (1) Pro proteger individuos de bon sanitate—individualmente o in gruppos—contra le invasion de specific organismos. (2) Pro prevenir secundari infectiones bacterial in personas acutemente malade con morbos pro que agentes antimicrobial non as efficace. (3) Pro reducer le risco de infectiones in patientes con varie typos de morbo chronic. (4) Pro inhibir

le propagation de morbos ab localisate areas de infection o pro prevenir infection in general in personas exponite a traumas accidental o chirurgic.

Le grado de successo obtenite per chimoprophylaxis ha variate con le objectivo de su application. Chimoprophylaxis ha succedite le melio quando su objectivo esseva le prevention de specific morbos. Assi le prevention de invasion per le streptococco beta-hemolytic es facilemente attingite per le administration de penicillina. Le risco del recurrentia de febre rheumatic pote esser grandemente reducite o mesmo eliminate completemente per le uso diurne de penicillina o sulfadiazina. Le administration de sulfonamidos es multo efficace in prevenir infectiones per le bacillos de dysenteria o per meningococcos in individuos in bon stato de sanitate. Chimoprophylaxis ha succedite le minus quando su objectivo esseva prevenir infectiones in general. Le risco de complicationes infectiose resultante del invasion de bacterios in casos de poliomyelitis, rubeola, pneumonia "viral," infectiones del vias respiratori superior, chirurgia elective, etc., es reducite per multo pauco, si del toto, per le uso de agentes antibacterial. Le organismos que es le plus frequentemente responsabile pro infectiones occurrente durante un curso therapeutic de antibioticos se monstra in multe casos difficile a eradicar per medio del nunc disponibile drogas. Le valor de chimoprophylaxis in dysfunctionamento cardiac, coma, accidentes cerebrovascular, parturition normal, etc., remane a determinar, sed le datos usque nunc colligite pare indicar que ille valor de chimoprophylaxis es basse o non-existente.

Le mesme non-desirate effectos que occurre in le administration de antibioticos pro objectivos therapeutic es etiam a observar quando iste drogas es administrate a individuos sin infection active. Le risco del disveloppamento de reactiones lateral e le consequente difficultates debe semper prender se in consideration quando on plana un programma de chimoprophylaxis. In casos in que le uso de agentes antibiotic como protection anti-infectiose es demonstratemente efficace, ille risco pote currer se con plen justification. In casos in que le efficacia del prophylaxis es questionabile, il es necessari studiar cautissimemente omne aspectos del situation ante que le tractamento es initiate, e le beneficios a expectar debe esser ponderate in comparation con le possibile periculos. Quando le sperate efficacia de un curso chimoprophylactic es sin demonstration per previe experientias, on non deberea usar lo.

Le campo del chimoprophylaxis require studios plus exacte e plus critic que le studios usque nunc dedicate a illo. Il es un frappante facto que le areas clinic in que prophylaxis anti-infectiose ha essite usate le plus extensemente es areas in que su uso se justifica principalmente per impressiones clinic plus tosto que per factos establite in le curso de investigationes controlate.

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MICROBIAL RESISTANCE TO ANTIBIOTICS * †

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EVER since the introduction of antibiotics there has been considerable interest in the problems stemming from the resistance of certain species or strains of bacteria. Because of the experience with the sulfonamides before penicillin became available, many workers felt that the development of resistance would become a major problem in a short period of time, while others adopted a wait-and-see attitude. During the intervening years the picture has been complicated by (1) the observation that new infections caused by resistant organisms may be superimposed on preëxisting infections, and (2) the introduction of new antibiotics. However, it is now possible to reach some conclusions regarding the mechanisms and extent of microbial resistance to antibiotics. It is the purpose of this paper to review the general principles as illustrated by several specific examples.

TABLE 1

Bacterial Mechanisms That Have Been Postulated to Be of Importance in the Development of Resistance * to Antibiotics

I. Ability to bypass the antibiotic.

† A. Naturally resistant organism—few if any clones or strains sensitive.*
B. Organism becomes resistant while exposed to antibiotic.

1. Adaptation—nonhereditary change in metabolism that allows persistence in face of antibiotics.
2. Mutation—hereditary metabolic changes brought about by exposure to antibiotic.
3. † Overgrowth of preëxisting mutants. Hereditary metabolic change present in a very infrequent clone at the time antibiotics are started.

II. Ability to produce antibiotic inactivating enzymes.

† A. Quantitative relationship between rapidity of enzyme production and bacteriologic effect of antibiotic.

* In this paper a strain is considered to be sensitive to an antibiotic when the minimal inhibitory concentration (m.i.c.) as determined in vitro is obtainable in the patient's tissue with usual doses of that antibiotic. Resistance includes those strains with a m.i.c. greater than this.

† Principal mechanisms which have been documented.

When patients are treated with antibiotics the appearance of resistant bacteria is related to the ecology of the microbes, the action of the drugs, and the nature of the process in the host and host population. As seen in table 1 and figure 1, several possible mechanisms have been postulated in

* From the Symposium on Infection, presented at the Thirty-sixth Annual Session of the American College of Physicians, Philadelphia, Pennsylvania, April 29, 1955.

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† Collection of original data used in this paper supported in part by research grants from Lederle Laboratories Division of American Cyanamid Company, Pearl River, New York, Charles Pfizer Co., Brooklyn, N. Y., and Abbott Laboratories, North Chicago, Illinois.

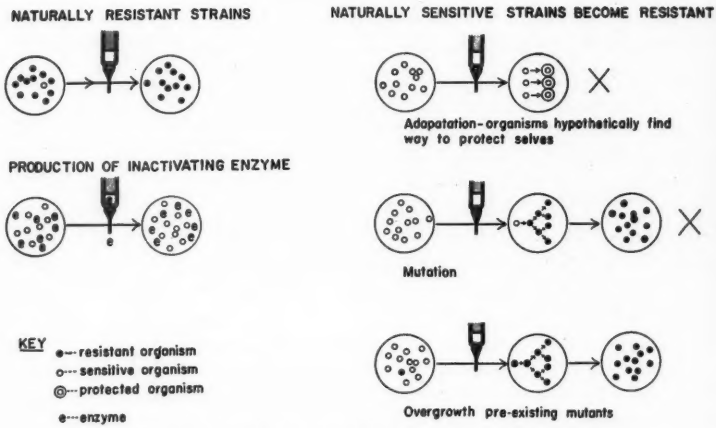


FIG. 1. Bacterial mechanism postulated to be of importance in the development of resistance.

the metabolism of the bacteria which conceivably lead to resistance. In spite of the fact that several distinct groups of antibiotics have been introduced, besides the fungi and the viruses, there are still some species or strains of bacteria which are naturally resistant to almost all available drugs in the concentrations obtained from the dose which can be administered. Notable among these are strains of Proteus, Pseudomonas, *Micrococcus pyogenes,* and some other gram-negative rods in the family enterobacteriaceae. Among these resistant strains of bacteria there is a large group in which the resistance to several of the antibiotics is great enough that these drugs are essentially useless in therapeutics. In addition, there is a second group in which there is relative resistance which requires the use of a large dose of one or more antibiotics. Most strains of enterococci, some of the *Streptococcus viridans* and some of the gram-negative rods fit into the latter group.

In spite of an early belief that clones of microbes could become resistant by undergoing adaptive hereditary or nonhereditary changes which would allow their growth and multiplication in the presence of the antibiotic, these phenomena have not been documented sufficiently for one to be sure that they occur. On the other hand, there has been repeated evidence that with all antibiotics some clones are more resistant than others.[1, 2] This difference is transmitted to successive generations and so, when a large number of clones are grown in the presence of the appropriate concentrations of antibiotics, there is a progressive favoring of the more resistant clones, which therefore persist and become predominant. When the differences in sensitivity between clones are not great, increases in resistance occur slowly and by small increments. On the other hand, when there is a wide spread

of susceptibility among clones, the highly resistant clones tend to predominate in a short space of time and the increments are large. In the laboratory it has been possible to make strains of almost all species resistant to practically all the commonly used antibiotics either by small or large steps. However, some strains, particularly the ones that have gone through the slow, small-increment process, have shown a loss of virulence during the procedure. Consequently, for the multiplication of resistant mutant clones to be significant in the production of antibiotic resistant infections in vivo, it is necessary that they maintain their virulence and overcome the host defenses. Such mutations are therefore not so important as they might otherwise have been.

The production of antibiotic-inactivating enzymes as a method by which bacteria can protect themselves is best illustrated by penicillinase production. This enzyme accounts for much of the high resistance of the gram-negative rods and of staphylococci to penicillin.

TABLE 2

Factors in Antibiotic Activity of Importance in the Determination of the Frequency of Resistant * Infections

I. Range of activity against multiple strains.

* A. Interference with bacterial ecology allowing superinfection by naturally resistant organisms.

* B. Limited range decreases number of infections which can be treated.

* II. Completeness of activity at an obtainable concentration against all clones in inoculum.

* III. Susceptibility to inactivating products produced by microbes.

* See table 1.

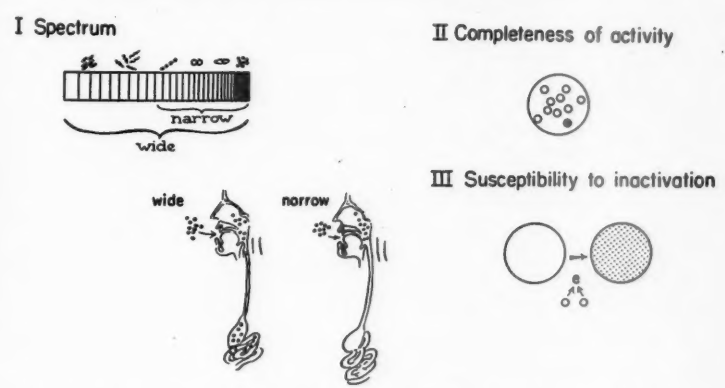


FIG. 2. Factors in antibiotic activity of importance in determination of frequency of resistant infections.

Factors which pertain to the different antibiotics that are important in the occurrence of resistant infections are listed in table 2 and figure 2. The range of activity of a given antibiotic is the most important factor in determining the occurrence of resistant microörganisms. Obviously, when a drug has a range as limited as penicillin, many organisms are resistant to it. On the other hand, even though the drugs with the broadest spectra are not effective against all organisms, they are sufficiently effective to alter profoundly the host's "normal" flora and to allow those organisms that are resistant to become predominant in areas such as the mouth, intestinal tract and genital mucosa. In a small number of patients such implantations or predominance of implanted organisms causes serious infections.

Some antibiotics, of which streptomycin is the most important example, have been shown to be ineffective even in high concentrations against a rare clone in many bacterial cultures,[3, 4, 5] provided the inoculum size is large. Consequently, the rapid multiplication of the resistant forms is of great importance and, if unchecked by the host's defense, will generally result in the infection's ultimately becoming resistant to the action of the drug.

With streptomycin, many drug failures are caused by infection with a strain of organisms in which almost all clones are originally sensitive but in which there is rapid conversion to a predominance of resistant clones. Erythromycin, particularly in the case of staphylococcus but also with other organisms such as *Streptococcus viridans*, seems to have a similar propensity.[6, 7] We have had occasion to study three patients in whom staphylococci of the same phage type recovered from the blood before and after the use of the drug have become resistant while the drug was being used. In

TABLE 3

Factors in Host and Host's Environment in the Development of Resistance

I. Host.

A. Anatomic deformities.

1. Allow implantation of resistant pathogens of low virulence.
2. Cause failure to destroy resistant clones if such are present.

B. Interference with defense mechanisms such as phagocytosis, antibody formation, antibacterial metabolitis, and so forth.

1. Allows implantation of resistant pathogens of low virulence.
2. Causes failure to destroy resistant clones if such are present.

C. Other therapies suppressing immunity.

1. Allow implantation of resistant pathogens of low virulence.
2. Cause failure to destroy resistant clones if such are present.

D. Mixed and chronic infections.

1. Resistant strains replace sensitive.

II. Environmental factors.

A. Carrier rates of resistant organisms in close contacts determine incidence of implantation.

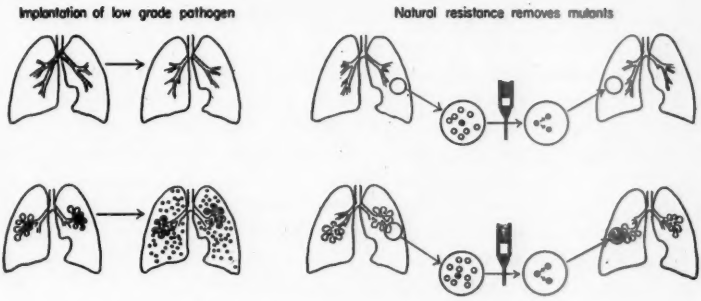
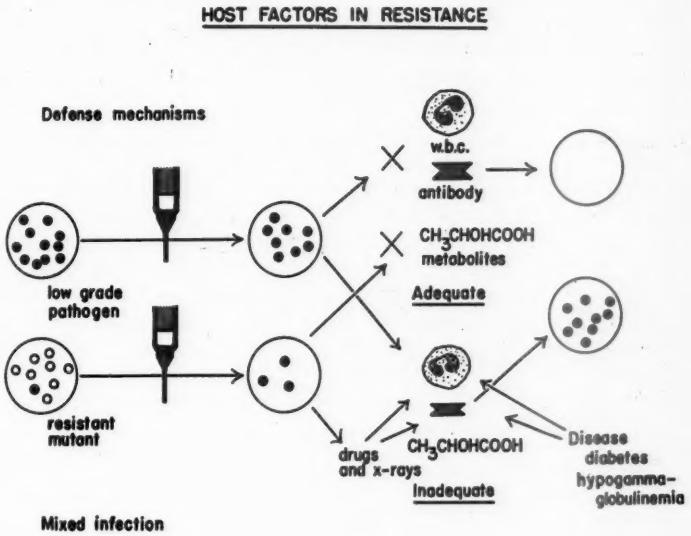


FIG. 3. Host factors of importance in development of resistance.



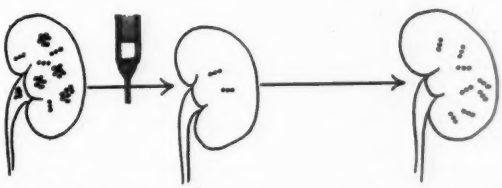


FIG. 4. Host factors of importance in development of resistance.

vitro, the evidence that clones resistant to erythromycin occur regularly in large inocula is equivocal, however.[8, 9]

Besides penicillinase production by staphylococci, and many gram-negative rods, other changes resulting from bacterial metabolism, such as the lowering of the pH in inflammatory exudates, may interfere with the action of some antibiotics, such as streptomycin, which are most effective in alkaline media.

In table 3 and figures 3 and 4 are listed factors in the host and the host's environment which encourage the occurrence of resistant infections. Most of the common acute infections are caused by highly pathogenic organisms which infrequently develop resistance [10] to antibiotics. On the other hand, frequent among the problems encountered in clinical practice are those associated with lowered host resistance, in which the resistant, partially-saprophytic organisms implant at new sites or become predominant when they are present in mixed infections. The occurrence of Pseudomonas or Proteus bacteremias while patients are receiving tetracycline antibiotics for chronic urinary or respiratory tract infections is typical. Closely related are the situations in which resistance develops rapidly from rare, highly resistant

TABLE 4

Factors which may contribute to origin of resistant infection	Infecting Organism				
	Myco. tuberculosis	Enterococci and some non-group A streptococci	Pseudomonas and Proteus species	*E. coli*; *A. aerogenes*; paracolon and intermediate forms	*M. pyogenes* var. *aureus*
I. Sensitive strains with rare resistant clones that proliferate, particularly to streptomycin and erythromycin	++++	+	+	++	+
II. Moderate natural resistance to available antibiotics		++++	+	+	
III. High natural resistance to available antibiotics	+++		++++	++	+
IV. Endogenous and exogenous implantations favored by antibiotics which remove competing organism		++	+++	++	++
V. Anatomic or other factors interfering with host immunity and eradication of infection	+	+++	++	+++	++
VI. Frequency in chronic mixed infections		++	++	+++	++
VII. Large reservoir of carriers with resistant strains (particularly hospital personnel)		+	+	+	++++

clones while antibiotics are being used. When the body's protective mechanisms are suppressed for anatomic or other reasons, the resistant clones which are not destroyed by the body may multiply. Such a factor may be a reason why tubercle bacilli develop resistance more easily in chronic cavitary tuberculosis than in the acute exudative variety.[11] Similarly, secondary infections with resistant organisms have occurred while one or more antibiotics were being used along with one of the 17-hydroxycorticoids.[12] Of considerable interest concerning the frequency of implantation of resistant organisms is the frequency of contact with persons carrying resistant organisms that are potentially pathogenic. This has been documented in the case of the resistant staphylococci transmitted from personnel to patients.[13]

Table 4 summarizes the importance of some of the mechanisms discussed to the occurrence of five groups of infections which are frequently encountered and constitute the principal areas in which antibiotic resistance by the organisms causes clinical problems. In most of the other bacterial infections antibiotic resistance is not a general or important phenomenon, even when the disease takes on a chronic relapsing aspect. Such infecting organisms may never exhibit resistance to most of the antibiotics in common use, whereas others which are naturally resistant to several of the agents respond to an effective drug without resistance becoming an important consideration.

Among the five groups listed in table 4 two infections, those caused by the tubercle bacilli and by staphylococci, have been extensively studied (figure 5). They illustrate the extremes of the mechanisms involved: tubercle bacilli tend to develop resistance to drugs by multiplication of resistant clones; resistant staphylococci tend to appear by the spread of resistant strains from outside sources to the patient. The other three infections are not so well studied, so that the relative importance of the different factors is not so well understood. In the case of the enterococcus and some of the other non-group-A streptococci, however, the organisms are known to be sufficiently resistant that greater than average doses of each of the drugs are required to reach antibacterial concentrations in vivo. However, there has been relatively little tendency for strains to increase in resistance while the patient is being treated, although it has been reported for penicillin [14] and erythromycin.[6, 7] From the frequency with which the development of resistant strains has been observed, compared to the time period during which the drugs have been used, the indication is that the phenomenon is most important with erythromycin and streptomycin, which correlates with the rapidity of the process in vitro.[8] Enterococci are not frequent primary pathogens, however, and the occurrence of infection depends on such factors as fecal contamination of wounds, spread by personnel to the respiratory tree following tracheotomy, infection of damaged heart valves following rectal surgery, and the persistence after therapy in mixed urinary tract infections. It should be emphasized that these organisms are only moderately resistant and consequently, by increasing the dose of peni-

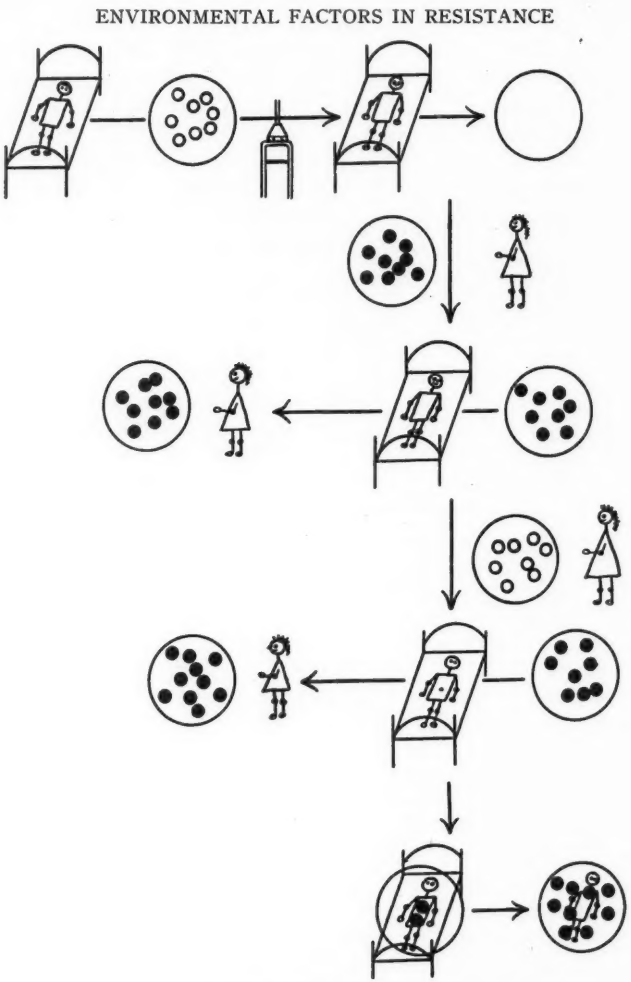


FIG. 5. Transmission patterns of resistant staphylococci.

cillin or using maximal doses of the other agents or combinations of agents, the infections are generally treatable. However, in some situations, particularly pyelonephritis, relapse is frequent even after large doses, and prolonged treatment is not uniformly successful.

With respect to Pseudomonas and Proteus, the situation is characterized primarily by a high degree of resistance of most of these strains to all of the

antibiotics and a moderate resistance of the remaining few strains. Sensitivity of Pseudomonas to polymyxin is the only bright spot in the treatment of these infections, and it is clouded by the limitations on the dose of the drug because of its toxicity. In our hands the nitrofurans have not been of great benefit in Proteus infection. Again, as indicated, these organisms are not frequent primary invaders, but are important in superinfections, mixed infections, and spread by personnel through open portals, particularly to patients with decreased defenses.

The other gram-negative rod infections differ in that there are fewer naturally resistant strains, and the overgrowth of clones resistant to streptomycin is relatively more important. The types of infection and host usually attacked are similar to those in which Pseudomonas and Proteus are involved. Cure of infection with any of the gram-negative rods mentioned is sometimes impossible, even when several agents are used for long periods of time.

Considerably different from the former groups is the situation with *Mycobacterium tuberculosis*. This organism has been resistant to most of the agents used effectively against other bacteria. The major exceptions are streptomycin and oxytetracycline. However, the organism is moderately resistant to the latter; consequently, large doses are required and results are limited. On the other hand, several other agents which have activity for little else than the tubercle bacilli are extensively used. Isoniazid, para-aminosalicylic acid and viomycin are some of these. Among the drugs introduced for the treatment of tuberculosis, only streptomycin and isoniazid have been potent enough to exert marked effect when used alone, but the effects of each have been limited by the overgrowth of resistant clones and the ultimate development of resistant infection. It has been well substantiated that organisms resistant to streptomycin retain their virulence, and that once they predominate the further use of streptomycin is relatively valueless.[15] There is considerable evidence that many of the strains that develop resistance to isoniazid lose their pathogenicity. However, the worsening of the clinical state with the appearance of isoniazid-resistant strains in the sputum of the patient receiving the antibiotic constitutes strong evidence that they are not simple saprophytes. It is now felt that certain INH-resistant strains are pathogenic if catalase is produced.[16]

Other factors than the ability of the organisms to develop resistance to the drugs are of some importance in resistant tuberculous infections. As mentioned previously, the type of lesion is one of the factors of importance in the development of resistant strains, the patient with cavitation being more likely to develop resistant strains in a given period of time. Moreover, organisms have been shown to be resistant in one lesion and not in others in the same patient.[17] Although initial infections by streptomycin-resistant strains have been reported, this has not been an important problem.

One of the most pathogenic organisms with which the problem of resistance has been encountered has been the staphylococcus. The mechan-

isms by which this organism becomes resistant illustrate several of the routes previously discussed (figure 5). While it is true that an increase may occur in the minimal inhibitory concentrations of penicillin, erythromycin, streptomycin, chloramphenicol, chlortetracycline and oxytetracycline in strains of staphylococci isolated from a patient's blood before and after receiving the appropriate drug, the phenomenon is infrequent. We have observed it at least once with all the antibiotics mentioned. Contrary to the situation in

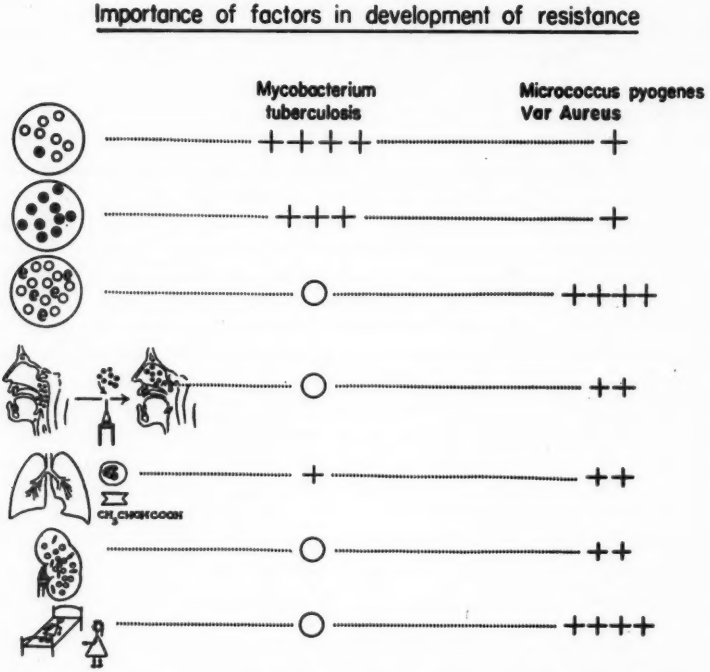


FIG. 6. Comparative mechanism for development of resistant *Micrococcus pyogenes* and *Mycobacterium tuberculosis* infection.

tuberculosis, however, this phenomenon has been the minor mode of origin of resistant infections. In a study of the importance of the development of resistant strains from the preëxisting nasal strains in patients receiving a tetracycline, penicillin or erythromycin, it was indicated that this phenomenon had little epidemiologic significance.[18]

Of more importance has been the fact that upon the introduction of each of the antibiotics there have been strains of staphylococci of high native resistance preëxistent in the community (figure 7). That the spread of these

strains has probably been the source of antibiotic-resistant staphylococcal infection has been indicated in the difference between infections acquired inside and outside of the hospital.[19, 20] A high percentage of the former infections is caused by resistant strains. Utilizing phage typing to identify strains, we have been able to show that personnel frequently transferred staphylococci from their nasal passages to those of the patient.[13] The frequency of transfer and the sensitivities of the transferred strains depended on the antibiotic that the patient was receiving at the time. Moreover, we have been able to show that such nasal implants have then invaded some patients, particularly those with lowered resistance caused by anatomic defects such as exfoliative dermatitis, tracheotomy, leukopenia and chronic infections, causing serious and even fatal infections. Some of the strains transferred from personnel to patient have considerable virulence and when implanted may, particularly with the help of the suppressive activity of a broad spectrum drug on the intestinal flora, lead to epidemics of severe staphylococcic enteritis among patients in some of whom there is little or no reason for suspecting a low capacity for resisting infection. The fact that the frequency of implantation and the pattern of sensitivities to antibiotics of the implanted staphylococci depend on the nature of the staphylococci in the carriers who have contact with an individual has been demonstrated by the fact that not only do the flora change in the patient upon admission to the hospital toward resistant flora, but also upon discharge the flora revert toward the pattern existing in the family. The unique influence of the hospital was illustrated by the fact that it was necessary to continue to use the antibiotic in the hospital in order to maintain among the carriers a high percentage (over 50%) of resistant strains.[21] This was true because approximately 60% of the carriers at any one time were transient carriers[22] (i.e., for less than one month), and consequently, if there were few patients receiving an antibiotic and therefore few who preferentially implanted, there were fewer resistant strains for the transient carriers to re-implant. This means that when a given drug is removed from the hospital and another drug used in its stead, the incidence of the resistant strains among carriers drops precipitously to the unused drug and rises similarly to the used drug. However, since the remainder of the carriers lose their strains very slowly (1% to 2% per month), the change in the carrier pool is very gradual after the drug has been removed for a short period of time.

In essence, then, the problem of bacterial resistance to antibiotics may be traced to organisms which were never sensitive to the drug being considered. The difference between a rare, resistant clone to the antibiotic which persists and overgrows under the influence of the antibiotic and is subsequently transferred as a predominant clone type to another patient is somewhat similar epidemiologically to an organism which consists primarily of resistant clones, the spread of which in the community is favored by the use of the antibiotic. The other factors considered are common to both

problems, with only quantitative differences. Thus, different antibiotics have different propensities in each situation. The host factors which limit the ability of the natural defenses to eradicate resistant strains are equally important in both situations, but on a quantitative basis carriers of resistant strains have a somewhat greater significance than carriers of strains with rare resistant clones.

As has been indicated, the problem of resistant infections has not been as great as it was once feared it might become. However, the five groups of bacteria described in table 4 can and do cause considerable hardship, disability and death. It can be truly said that in some of the areas we have reached the limiting factor of currently available antibiotic therapy. However, several general principles of therapy can aid in the minimization of the problem (table 5). The problem of how efficacious combinations of the

TABLE 5

Methods of Minimizing Difficulties from Antibiotic Resistant * Infections

I. Combinations of drug.
   a. Limit multiplication of resistant clone.
   b. Limit spread of resistant strains in a closed community.
II. Introduction of new drugs.
III. Gradual return of sensitive clones and sensitive strains after a drug usage has been decreased.
IV. Reducing the use of all antibiotics to a minimum.
V. Use of minimal effective dose and limited antibacterial spectrum.
VI. Careful bacteriologic studies before treating individuals with chronic infections and/or mixed infections.
VII. Treatment only for evidence of infection and not for presence of bacteria in chronic nontuberculous infection.
VIII. Remedy of underlying anatomic, immunologic or metabolic defect when possible.
IX. Nursing precautions to avoid interchange of organisms between personnel and patients

* See footnote, table 1.

drugs may be in reducing the incidence of resistant strains is still not clear. In the case of the resistant clone which multiplies under the effect of a single drug, such as streptomycin or erythromycin, a second drug, even one that is not as completely effective as the first, may definitely limit overgrowth by the resistant clone. This has been best established in tuberculosis, where para-aminosalicylic acid, a relatively ineffective drug, has potentiated the effect of streptomycin. In the treatment of tuberculosis now it is generally agreed that some combination of agents should be used routinely. Similarly, in the treatment of resistant staphylococcal infections, one could try combinations of antibiotics such as erythromycin plus a second agent which, by in vitro studies, appears likely to be effective. Less information is available concerning the rôle of the use of multiple drugs in a hospital population or a similar closed community in the actual incidence of transfer of resistant strains. If a combination of drugs is used from the beginning, and there are very few, if any, organisms resistant to either, and these few

organisms are resistant to only one of the drugs, not to both, then the use of an effective combination of drugs in hospitalized patients should reduce markedly the problem of transfer between personnel and patient. If, on the other hand, a large number of organisms are already resistant to one of the agents, introduction of a combination of agents would not suffice, simply because it is likely that development of resistance to the second drug would follow the same pattern as it would were the first drug to which the organisms are already resistant not included. Our results with penicillin and Aureomycin suggest that, while the quantitative factors involved may delay slightly the occurrence of implantation with organisms resistant to both antibiotics, these do occur and increase quite rapidly when the organisms are already resistant to one or both of the antibiotics.[13] When some of the organisms are resistant to both antibiotics, the pattern followed is very similar to that for the use of a single drug to which some of the organisms are sensitive and some are resistant.

The introduction of new drugs to which the number strains with resistant clones or the number strains in which most clones are resistant are low, is to be hoped for. While new drugs are being used in the community there may be a shifting back from the number of resistant strains in the community toward the pre-introduction level for the older drugs. Such data have been suggested by Finland in his study of gonococci [23] in relation to sulfonamides. In these studies, after a prolonged period during which the sulfonamides had not been used extensively in treatment of gonorrhea, there is some evidence that the organisms are reverting to their original level of sensitivity to sulfonamides.

Reducing the use of all antibiotics to a minimum to limit the opportunities for spread of resistant strains is obviously of importance. Since the number of persons getting antibiotic treatment in a hospital community is of importance in the maintenance of a large carrier pool of resistant organisms, limitation in the use of the drug would greatly curtail this problem. In addition, the use of the minimal effective dose of the antibiotic, and particularly limiting the range of activity to the species requiring treatment so that the normal flora of the patient can be maintained as undisturbed as possible, are of considerable importance in interrupting the epidemiologic spread of the organism, as well as in reducing the incidence of such infections as staphylococcic enteritis. The problem is particularly severe in chronic illnesses where the superinfections and overgrowth of flora are most alarming and difficult to deal with. In these infections one should treat specifically for a minimal time with a minimal dose in order to get the maximal therapeutic results and decreased incidence of implantation. In this connection, appropriate bacteriologic studies are most important before treating individuals with chronic infections and/or potentially mixed infections. It has been our policy not to treat individuals with chronic infections such as bronchiectasis or pyelonephritis merely because positive

cultures have been found in the urine or in the tracheobronchial tree. It is felt that after a period of time it is practically impossible not to have other organisms replace those currently present. Consequently, an attempt should be made to evaluate the severity of the process going on in relation to the organisms being obtained and, if it appears that treatment is necessary, one should then make every attempt to eradicate the particular organism or group of organisms that seem most likely to be involved. The strain removed almost invariably will be replaced by some other organism, but the patient may greatly improve. On the other hand, the converse is true: if one treats organisms for the sake of treating organisms it is possible that the freshly implanted organism may cause more serious damage and the patient be worse for the course of therapy.[24] It is also obvious that many of the problems of resistance are concerned with situations in which there is a basic lack in the defense of the host due to the implantation of resistant strains either from the environment or from the overgrowth of resistant clones, and that remedy of the underlying anatomic, immunologic or metabolic defect should be undertaken whenever possible. Thus, the lessening of the ketosis in diabetes, the use of surgical drainage, and proper postural drainage and similar procedures are always of benefit in lessening the incidence of resistant infections. In addition, because of the evidence that the personnel in hospitals are important in the spread of resistant strains and in the production of infections by such strains, it is advisable that aseptic nursing precautions be used, particularly in those situations where resistant infection is apt to become an important problem, such as the patient with chronic pulmonary disease or chronic urinary tract disease, and in operations such as those for osteomyelitis. Treatment of patients with chronic respiratory tract disease might be safer in the home than in the hospital.

Summary

1. An estimate has been made of the extent of the problem of antibiotic-resistant organisms as a cause of bacterial infections. It has been shown that, while this problem is not as serious as it might have been, there is considerable evidence of a definite limitation of the effect of the antibiotics because of resistant organisms.

2. Most of the infections are caused by organisms which either had a small number of resistant clones at the time of the introduction of an antibiotic or else had many resistant strains already existing at the time the antibiotic was introduced. In each case the propagation and spread of the organisms resistant to the antibiotic, whether from a rare clone or from strains already present in the community, have created the current situation, by the favorable action of the antibiotic in question on the dissemination and multiplication of such organisms.

3. The importance of the host factors in allowing resistant infections to become established and to persist has been emphasized.

4. Infections with *Mycobacterium tuberculosis* enterococci and some related, relatively resistant non-group A streptococci, Proteus and Pseudomonas infections, other gram-negative rods in the *Escherichia coli,* Aerobacter, paracolon and intermediate group and *Micrococcus pyogenes* var. *aureus* infections, have been listed as the principal groups of bacteria which at the present time constitute a clinical problem. Each of these infections has its own peculiarities as far as the relative importance of the host, the site of the infection, the importance of different antibiotics and the environment in which the patient has been studied are concerned.

5. A contrast has been made between the development of resistance of *Mycobacterium tuberculosis,* in which the resistant clone which multiplies under the influence of the antibiotic is most important and in which spread from one individual to another is relatively unimportant, and *Micrococcus pyogenes* var. *aureus,* where the development of resistant strains in a patient has not been of so much significance as the dissemination of resistant strains from personnel to patients and vice versa.

6. Nine suggestions have been made to decrease the severity of the problem of antibiotic resistant infections.

Summario in Interlingua

Es presentate un evalutation del problema de organismos resistente a antibioticos como causa de infectiones bacterial. Il resulta que le problema es minus serie que on haberea potite timer sed il ha definite indicationes del limitation del effectos de antibioticos in consequentia del facto que il ha organismos que es resistente a illos.

Le majoritate del infectiones es causate per organismos le quales habeva, jam al tempore del introduction de antibioticos, o un parve numero de clones resistente o un considerabile numero de racias resistente. In ambe casos le propagation e dissemination de organismos resistente a antibioticos—tanto illos descendite ab un clon exceptional como illos representante jam existente racias intra le communitate—ha resultate in le presente situation, un disveloppamento que ha devenite possibile a causa del favorabile effecto del antibioticos super le conditiones de propagation e dissemination del organismos in question.

Es a sublinear le importantia del factores in le systema del hospite le quales es responsabile pro le facto que resistente infectiones pote establir se e que illos pote perdurar.

Le lista del principal bacterios que constitue al tempore presente un problema clinic a causa de lor resistentia a antibioticos include *Mycobacterium tuberculosis,* enterococcos e alicun relativemente resistente streptococcos affin non pertinente al gruppo A, organismos del generes *Proteus* e *Pseudomonas,* altere bastonettos a Gram negative in le gruppos de *Escherichia coli* e *Aerobacter* como etiam in le gruppos paracolonic e intermediate, e *Micrococcus pyogenes* var. *aureus.* Le infectiones con cata un de iste organismos ha lor peculiaritates in re le relative importantia del hospite, le sito del infection, le importantia del varie antibioticos, e le ambiente in que le patiente es studiate.

Es signalate le contrasto inter le disveloppamento de resistentia in *M. tuberculosis* e in *M. pyogenes* var. *aureus.* In *M. tuberculosis* le clon resistente que se multiplica sub le influentia del antibiotico es importantissime durante que le dissemination ab un individuo al altere es relativemente pauco importante. In *M. pyogenes* var. *aureus,* del altere latere, le disveloppamento del racia resistente intra le patiente es minus sig-

nificative que le dissemination del racia resistente ab le patiente al personal o ab le personal al patiente.

Le methodos disponibile pro reducer le difficultates del infection per organismos resistente a antibioticos include le uso de drogas in combination, le uso de doses a efficacia minimal de drogas a spectro limitate que es a seliger in le caso de patientes con chronic morbos super le base de exacte studios bacteriologic, le tractamento de defectos subjacente, e precautiones imponite al personal pro evitar le dissemination de bacterios de racias o clones resistente.

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THE MANAGEMENT OF INFECTIONS OF THE URINARY TRACT*

By Edward N. Cook, M.D., *Rochester, Minnesota*

There is no other urologic complaint which receives a lesser degree of competent management than do infections of the urinary tract. This sad state prevails in spite of the fact that our means of diagnosis in such conditions are equal or superior to those applying to almost any other disease to which the human being falls heir. Moreover, we do have means of managing most of these situations if we will but use the simplest of diagnostic methods, supplemented at times by more detailed technical procedures.

The Exercise of Common Sense

Perhaps my approach to this discussion appears to be somewhat elementary. If so, I beg your indulgence. What I have to say is of a basic nature, because it pertains to the methods used in our daily clinic practice, methods which have stood the test of time and which, despite their simplicity, are nonetheless sufficient to produce an accurate diagnosis and adequate treatment in most instances.

To begin with, we must be certain an infection is present. Next, if it is found to be present, we must have some knowledge of what type of infection it is. These seemingly unimportant basic facts mean that we must be ever-cognizant of the fact that many infections of the urinary tract actually are secondary to some coexisting pathologic entity which could preclude any satisfactory management of the problem of the infection by itself. For more than a score of years we have repeatedly emphasized the importance of evaluating the efficacy of any therapeutic procedure in the light of whether it is being used to combat infection in an uncomplicated situation or in the face of the presence of stone, tumor, obstruction or chronic cicatricial changes in the kidneys so often present in a long-standing infection.

The Exercise of Individual Analysis

Careful evaluation of the history in an individual case and examination of a properly collected specimen of urine are absolutely essential. The complaints of burning on urination and frequent urination are a part and parcel of any urinary infection, with or without a complicating lesion. However, if these common symptoms are carefully discussed in the light of their rela-

* From the Symposium on Infection, presented at the Thirty-sixth Annual Session of the American College of Physicians, Philadelphia, Pennsylvania, April 29, 1955.

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tionship to the act of voiding, to any associated pain or distress, to any symptoms suggesting particular pathologic conditions such as pain in the flank, suprapubic discomfort, vaginal distress or dyspareunia, the examiner very frequently will be promptly rewarded by the proper lead. When this lead has been elicited, the patient may be saved time, suffering and expense from the start. The point is that in the face of, let us say, coexisting hydronephrosis with stone in the involved kidney, any protracted therapy directed toward eradication of an infection in the urinary tract will be of no avail. First things come first, in urologic practice as well as in formal logic.

Now, let us suppose that the patient complains of burning on urination. If this occurs preceding the act, and is associated with urgency of varying degree, it is likely to be caused by trigonitis alone or to be an accompaniment of cystitis. Burning during the passing of urine usually represents urethritis per se. If, however, the burning occurs after voiding, then the examiner should think of trigonitis in association with urethritis.

To continue the inquiry, let us say that this patient tells us that frequency accompanies the sensation of burning. Many times this is so, but at times frequency is the only complaint. When this is true, and when it is present day and night, it often is explained by the finding of interstitial cystitis, a rather severe distressing lesion of the bladder usually found in women. It may be accompanied by severe suprapubic pain or pain referred to the urethra, perineum or buttocks. The urine in these cases is microscopically normal and is sterile. Frequency of urination is pronounced. In such an instance, the most helpful question the physician may ask is, "Does urination relieve your distress?" These patients invariably will answer, "Yes, completely." Thus, the sifting-out of a simple complaint like frequency of urination can disclose the presence of something far more significant than the complaint itself.

These points are brought forward in an effort to illustrate how profoundly important and useful a detailed history may be in accurate evaluation of a patient's distress. When there is a suggestion of a coexisting pathologic condition, the patient is entitled to a detailed urologic study immediately. Years ago we were able to show that the results of therapy for infections of the urinary tract are more dependent on the presence or absence of a complicating lesion than on the infection itself. When the infection occurs alone, the results of any medication are far superior to those obtained when the infection is accompanied by stone, tumor, obstruction or the like. The advent of the new "wonder drugs" has not altered this concept in any degree.

Whenever I enlarge on the importance of a properly obtained specimen of urine, I almost feel that I am casting aspersions on the intelligence of the men I am writing for. That is surely furthest from my intent. I emphasize the point simply because there is rarely a week that goes by during which I am not confronted with at least one patient, usually a female, who has been taking countless dollars' worth of antibiotic agents for an infection of the

kidney or bladder which does not exist. Of course, there can be no improvement in her situation by way of the pharmacist's magic box. What happened was that studies of specimens of voided urine revealed pus and organisms, and so the wonder drugs were prescribed. Often, in such cases, clinical curiosity would disclose cicatricial or granular urethritis. Had care been taken to obtain a specimen of urine by catheter, that specimen would be found to be normal and sterile. Where, then, is the "infection of the bladder"? The true condition can be relieved when proper local therapy is instituted.

To obtain and to examine a specimen of urine accurately from the female, it must be taken by catheter and collected with the utmost cleanliness. To obtain a specimen from the male, the two-glass test should be employed after the glans penis and the external meatus have been thoroughly cleansed. The properly collected specimen should then be centrifuged, and the sediment examined under the high-dry objective of the microscope. Here the presence of pus, erythrocytes, spermatozoa, crystals or debris should be noted. The smear should then be dried and stained by Gram's method to demonstrate or rule out any organisms. If organisms are present, they can be readily divided into two great groups: bacilli or cocci. Bacilli usually are gram-negative and cocci as a rule are gram-positive. This information, so easily and so quickly obtained in your own office while the patient is waiting, in the majority of instances will provide all that is necessary for satisfactory treatment of infections of the urinary tract.

Culture of specimens of urine and subsequent identification of the actual organisms present are not necessary in most cases. Such a procedure undoubtedly is of great value at times, but even then it has to be done in conjunction with Gram's staining.

One morning recently I was called in consultation to see two patients who had had surgical treatment. Culture of the urine done postoperatively had produced Proteus organisms in one instance and Pseudomonas organisms in the other. In neither case had there been study of the urinary sediment or Gram's staining. Since neither patient seemed in any distress, I deferred treatment and ordered a microscopic analysis of the urinary sediment, Gram's staining, and another culture in each case. The next day it was found that results of the entire study in each case were negative.

Why, then, did I ask for the studies? First, I did so because I know that the assurance of absolutely sterile technic is a problem at best, and I wanted to be certain it had been employed. Second, I did so because I know that both the organisms first reported frequently are contaminants. Another such organism is *Streptococcus faecalis*. It is true, however, that all three can cause trouble. *Str. faecalis* is perhaps the only organism that frequently can be identified by Gram's staining alone. It is gram-positive, occurring in chains, and spheroid, with its long axis in the line of the chain. Also, there is a light-refraction streak down its center. These facts are

worth remembering, because if this organism is present, it usually requires particular treatment.

When should we insist upon a complete urologic investigation for the patient who presents symptoms of an infection of the urinary tract? By no means need complete investigation be routine. However, if associated symptoms suggest a coexisting lesion in the urinary tract, complete urologic study should be done at the start. Moreover, whenever two or three courses of therapy have not brought about eradication of the infecting organism, or the patient's symptoms are not relieved, complete investigation is in order.

The Therapeutic Jungle

The place of studies of sensitivity in respect to the efficacy of the various chemotherapeutic and antibiotic compounds against a particular organism is worthy of comment. Studies of sensitivity of organisms should not be done routinely. They are time-consuming and expensive, and in most instances contribute no additional help. However, when an infection has proved resistant to the usual methods of therapy, studies of sensitivity in conjunction with complete urologic study, including urography and cystoscopy, may prove of great value.

Perhaps all of us have noticed at times an apparent change in the resistance of certain organisms to the various drugs or antibiotic agents. A decade ago, for instance, approximately 90% of the staphylococcic infections we saw were susceptible to penicillin. Today only about 25% respond to this agent. More recently, erythromycin has been highly efficacious against staphylococci, but of late we are finding more forms of this organism which cannot be destroyed with this drug.

Personally, I am thoroughly convinced, after more than 22 years' experience in treating infections of the urinary tract, that there is no rule-of-thumb and can be none. Each patient's infection is a different problem, and while certain generalizations are permitted, they must be weighed in the light of the individual case.

Today we are most fortunate in having a number of drugs from which to choose. I say "fortunate" because it very often happens that one or two, or even more, may be useful in a single case. My custom is to choose one which is known to be effective against a fair number of different organisms. The first choice generally is one of the sulfonamides (7½ gr. given four times a day for one week), because they are cheap and quick-acting and produce a minimal number of toxic reactions in the dose usually prescribed for infections of the urinary tract. Nitrofurantoin (Furadantin) and the tetracyclines also are broad-spectrum compounds, and they constitute an excellent sequel to sulfonamide therapy when the latter fails. Furadantin is relatively nontoxic. Nausea occasionally accompanies use of the agent, but it can be kept at a minimum when the drug is taken with meals—not

before or after—and the bedtime dose also given with food. Cutaneous reactions are rare. The usual dose is 100 mg. administered four times a day. The tetracyclines are not always well tolerated—nausea, vomiting and irritation of the lower bowel may result from their use. These effects occur less often when Terramycin or Achromycin is used. The dose of the two latter drugs is 250 mg. administered four times a day.

Penicillin today exerts its greatest effectiveness on the streptococci, exclusive of *Str. faecalis*. At times, when penicillin is administered with the sulfonamides, it may be of value against *Str. faecalis*. This combination also has proved to be of advantage against bacillary infections and against a number of staphylococcic infections. Between penicillin and streptomycin there is a synergistic relationship which seems to enhance the effectiveness of each of these drugs when they are used together as compared to when they are used alone.

Streptomycin alone is rarely indicated in the management of infections of the urinary tract. If it is to be used against bacillary infections, studies of sensitivity should be done first, and the effectiveness of the agent against the particular organism at hand should be demonstrated. Furthermore, if this drug is to be used, it must be used in an adequate dose, which would be 2 gm. daily for two or three days, followed by 1 gm. daily for two or three days more. Such a scheme is necessary because if streptomycin is to be effective, it must be given in an adequate dose before the organism develops a resistance to it. Manifestations of toxicity caused by streptomycin are not uncommon; they are well known to all.

As mentioned previously, erythromycin is of great value in most infections caused by gram-positive organisms, particularly staphylococci. It is of little or no value against those caused by gram-negative bacilli. Polymyxin is an extremely toxic drug which I feel should be used only against a urinary infection caused by Pseudomonas organisms and when the patient is gravely ill. It is the only drug which seems to have any real effectiveness against this particular organism. Nonetheless, it never should be used without a complete understanding of the symptoms of nephrotoxic and neurotoxic effects which may follow its use. Neomycin is another antibiotic agent of questionable value in urinary infections. It engenders a toxic reaction similar to that caused by streptomycin, and should be used only after studies of the sensitivity of the organisms involved have established its worth over other drugs.

Unfortunately, the most effective antibiotic agent thus far produced for use in this field proved to be toxic to the hematopoietic system in a very small percentage of cases. This agent is chloramphenicol. Instances of aplastic anemia have followed the use of this drug, but the actual incidence of that complication has been very low. More recently, studies suggest that much of the concern over this undesirable sequel may be eased. However, I still hold that we should proceed cautiously in the administration of

chloramphenicol, and never use it without frankly discussing the matter with the patient. Again, I believe studies of sensitivity should be carried out to prove the value of the agent in the individual case before it is used.

It is very difficult to evaluate most of the papers in the literature on the clinical use of these compounds. Clinicians, reporting their results, will say that a certain drug eradicated a certain organism in a certain percentage of cases, with absolutely no mention of whether the infection was simple and uncomplicated or whether a coexisting pathologic process was present. Unless these facts are set down, the results in such publications are of little value. Only too often we see patients who have been treated with one or another of these expensive drugs for months, yes, even years, when a silent stone was and still is present in the upper part of the urinary tract. To expect drug therapy to overcome such a condition is to ask for the impossible.

I should like now to call your attention to another gross error in clinical management. After prostatic operations carried out by any one of the various methods, there usually is some degree of residual posterior urethritis and prostatitis in the remaining part of the prostatic capsule. The urine in these cases frequently gives evidence of pyuria. This sign may be present for years, yet it seldom if ever will cause the patient any trouble. Nevertheless, the physician who detects this type of pyuria generally will prescribe one and then another of the antibiotic agents, which seldom will eradicate the infection.

It is true that oral medication has largely supplanted local therapy in the treatment of most infections of the urinary tract. Lavage of the bladder and instillations of a mild silver protein (Argyrol) are frequently of immediate value when the infection is acute. Furthermore, when the patients are females with trigonitis and urethritis, instillations of Argyrol, lavage of the bladder, the use of urethral suppositories and dilatations will prove very effective at times when the antibiotics are of no value. Parenthetically, we may observe that the antibiotic agents likewise have not helped in the treatment of chronic prostatitis or epididymitis.

Comment

The foregoing represents what I believe is a true evaluation of the present approach to management of infections of the urinary tract. The application of careful analysis in each situation, and the use of that gift of common sense which is the possession of every reasonable man, are the two impressive agents which will help the most. There is no place for dogma.

Summario in Interlingua

Il es necessari verificar le presentia de un infection. Si le facto del infection es establite, nos debe obtener certe informationes in re le typo de infection de que il se tracta. Nos debe semper rememorar nos que multe infectiones del vias urinari es de facto consequentias de coexistente entitates pathologic que pote blocar le efficacia

de omne tractamento directe del infection per se. Le exacte evalutation del historia de cata caso individual e le correcte collection e examination de un specimen de urina es absolutemente indispensabile. In le caso de femininas le specimen de urina debe esser obtenite per medio de catheterisation. In le processo on debe observar le plus alte grado de munditia possible. In le caso de masculos on debe servir se del essayo a duo vitros post que le glande e le meato externe es cautemente mundate. Postea le ben colligite specimen es centrifugate e le sedimento es examinate sub le appropriate objectivo del microscopio. Hic le presentia de pus, erythrocytos, spermatozoos, crystallos, o debris debe esser notate. Tunc le frottis es siccate e tincturate per le methodo de Gram pro demonstrar le presentia o absentia de organismos. Si organismos es incontrate, il es facile divider los in bacillos e coccos. Bacillos es normalmente a Gram negative e coccos a Gram positive. Si le caso es characterisate per symptomas associate que pare indicar coexistente lesion in le vias urinari, un complete studio urologic debe esser executate immediatemente.

Penicillina exerce hodie su plus grande effecto super le streptococcos, non includente *Streptococcus faecalis*. Streptomycina sol es rarmente indicate in le tractamento de infectiones del vias urinari. Polymyxina es un droga de extreme toxicitate e deberea usar se solmente in casos de infectiones urinari causate per organismos del genere *Pseudomonas* e quando le patiente es gravemente malade. Post operationes prostatic, executate secundo non importa qual methodo, il ha generalmente un certe grado de residue urethritis posterior e prostatitis in le remanente parte del capsula prostatic. In tal casos le urina revela frequentemente le presentia de pyuria. Iste symptoma pote persister durante longe annos, sed illo es rarmente le causa de ver difficultates. Lavage del vesica e instillation de un dulce proteina a argento (Argyrol) es frequentemente de adjuta immediate quando le infection in question es acute. In plus, quando le patientes es femininas con trigonitis e urethritis, bon resultatos pote esser obtenite per instillationes de Argyrol, lavage del vesica, le uso de suppositorios urethral, e dilatationes. A vices iste programma se prova efficace mesmo quando le antibioticos es sin valor.

A REËVALUATION OF SULFONAMIDE THERAPY *

By ELLARD M. YOW, M.D., *Houston, Texas*

IT is not difficult to understand the decreased interest in the sulfonamides following the introduction of penicillin, an agent which produced dramatic therapeutic results and which could be administered in unlimited amounts without evidence of toxicity. This came as an impressive relief after the trying years of carefully regulating the dose of the sulfonamides so as to maintain an effective level and yet remain within the relatively narrow margin between the toxic and therapeutic levels. Physicians were anxious to forget the difficulties encountered in the administration of large amounts of fluid and alkali, given in an attempt to prevent the precipitation of crystals in the renal tubules. The problems of agranulocytosis, aplastic anemia, hemolytic anemia, jaundice, dermatitis, drug fever, and the fear of the production of disturbances in collagen seemed to be things of the past.

During the 10 years following the discovery of penicillin, antibiotics were introduced with spectra covering all the pathogenic bacteria, rickettsiae, large viruses and spirochetes. Few problems remained, only the infections due to the smaller viruses, most of which were more troublesome than serious, and rare fungus infections.

In spite of the tremendous therapeutic success of the antibiotics, problems soon began to appear. At first an occasional patient was found to manifest evidence of hypersensitivity to penicillin in the form of a delayed serum sickness-like reaction or the earlier urticarial rash. Streptomycin therapy was associated with acoustic nerve damage and dermatitis, and its usefulness was often limited by the rapid development of strains resistant to its action. The tetracycline group of antibiotics as well as chloramphenicol often produce nausea, vomiting, diarrhea, and monilial infections of the intestinal and genital tracts. None of the antibiotics subsequently introduced has been as free of true toxic reactions as penicillin; and the antibiotics of the polypeptide group have a narrower margin of safety than sulfadiazine.

Today the incidence of allergic reactions to penicillin approaches 10%, and over 130 cases of severe anaphylactic reactions have been reported, of which 40 were fatal.[1] Blood dyscrasias have been associated with the administration of streptomycin and chloramphenicol, and probably with other antibiotics, with 44 deaths due to aplastic anemia. Serious infections due to staphylococci and the gram-negative bacilli, resistant to all antibiotics, are being observed with increasing frequency, and superimposed infections often develop during antibiotic therapy.

* From the Symposium on Infection, presented at the Thirty-sixth Annual Session of the American College of Physicians, Philadelphia, Pennsylvania, April 29, 1955.

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There can be no doubt that in almost every infectious disease, antibiotics are more active therapeutically than the sulfonamides. However, since it now appears likely that progress will be made less rapidly in the field of antibiotics, it seems appropriate that the laboratory and clinical investigations of the sulfonamides during the past 12 years be reviewed and an attempt made to determine the place of the sulfonamides in the treatment of infectious diseases today.

In 1941 penicillin was first used in the treatment of patients with staphylococcal and streptococcal infections. In the same year Roblin and co-workers [2] synthesized sulfadiazine. The results of the widespread clinical trial with this sulfonamide in 1942 and 1943 justified the earlier conclusions that sulfadiazine was generally the most satisfactory sulfonamide from the point of view of therapeutic effectiveness developed to that date. Higher blood levels were attained by the administration of the methylated derivative of sulfadiazine, sulfamerazine, but it and subsequently developed sulfonamides have not been shown to be more effective clinically when administered in equivalent doses.

During the past 10 years the major effort in the field of sulfonamide therapy has been in the control of the toxic complications associated with their administration. Most of the serious complications, such as hematologic disorders, had been reduced to less than 0.1% by the use of sulfadiazine, but the remaining serious complication of renal tubular irritation and blockage continued to occur in 2% of the patients following oral administration of the drug, and in a somewhat greater number following its parenteral use.[3] This complication could be reduced by maintaining a high output of alkaline urine, though in some patients with advanced renal and cardiac disease the increased sodium intake was undesirable.

The control of the problem of the renal complications associated with sulfonamide administration was approached from two points of view. Lehr [4] introduced the concept of combining sulfonamides on the basis that the saturation in the urine by one sulfonamide is independent of the concentration of another. Since each acts by the same mechanism there is an additive bacteriostatic effect when they are given in combination, but an independent solubility in the urine. Many combinations have been used, most of which have contained equal amounts of the relatively insoluble sulfadiazine, the rapidly absorbed sulfamerazine, and the relatively soluble sulfamethazine. More recently it has been recommended that the more soluble sulfadimidine (Elkosin) be substituted for sulfamethazine.[5]

The second approach to the problem of the precipitation of sulfonamide crystals in the renal tubules was the investigation of the highly soluble sulfonamides. Sulfisoxazole (Gantrisin) was introduced by Sarnoff, Freedman and Hyman [6] in 1946 and has received the widest clinical trial. Its solubility at a pH of 6 is approximately 260 mg. %, as compared to 25 mg. % of sulfadiazine. Occasionally crystals are seen in the urine, but there have

been no examples of tubular obstruction due to the precipitation of crystals, even in patients receiving as much as 24 gm. intravenously daily. Furthermore, hematuria due to the irritation of the tubules by crystals has been extremely rare.

More recently, other soluble sulfonamides have been studied experimentally and clinically, including sulfadimidine (Elkosin), sulfamethylthiadiazole (Thiosulfil) and sulfaethiadiazole. These drugs have not had sufficient use in systemic infection in this country for final evaluation.

Conflicting reports have appeared in the pharmacologic and medical literature regarding the relative merits of the sulfonamide mixtures as compared to the single soluble sulfonamides. This has resulted largely from the difficulty in studying quantitatively the effectiveness of sulfonamides in experimentally produced infections in animals and the limited number of clinical infections being treated today with sulfonamides alone. It seems likely, however, that sulfadiazine, sulfamerazine, sulfamethazine, sulfisoxazole, sulfadimidine and sulfamethylthiadiazole are equally effective in most instances where equivalent concentrations of the free drug are maintained in the tissues. There are some differences, however, in the rate of absorption, the rate of excretion, and the level attained on a given dosage schedule, as illustrated in figures 1 and 2. These differences affect mainly the method of administering the individual compounds and their dosage, and probably are not a significant problem if these factors are considered. It seems likely also that toxic manifestations of the recently developed sulfonamide mixtures and the soluble sulfonamides are extremely infrequent and probably occur in less than 0.1% of patients. Sulfadiazine does have a slight advantage over the others in that somewhat higher spinal fluid levels are attained. This problem has been satisfactorily handled in our experience by the administration of larger doses of the soluble sulfonamides parenterally

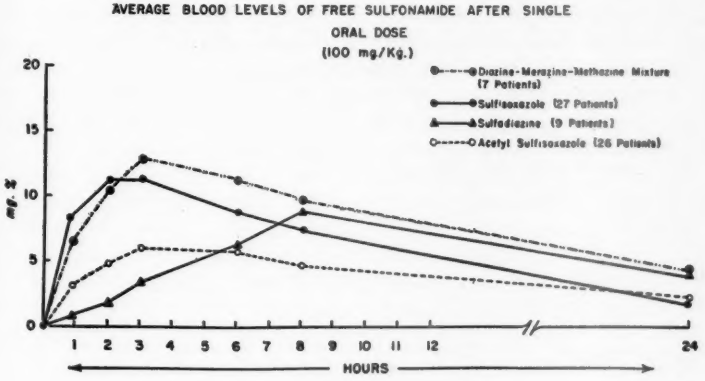

FIG. 1.

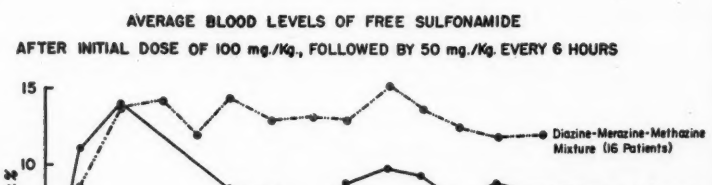

FIG. 2.

in patients with nervous system infections. The more soluble sulfonamides have certainly not replaced sulfadiazine if it can be administered under carefully controlled conditions, but the occasional occurrence of renal tubular blockage makes it less safe for widespread general use.[9]

During the earlier years of the antibiotic era the use of the sulfonamides dropped off strikingly, but since 1949 the increasing experience with the newer preparations provides information for an evaluation of their indications. It is now generally agreed that the sulfonamides are the preferred antibacterial agents in the management of meningococcal infections. Strains of meningococci clinically resistant to sulfonamides have not been encountered. Penicillin may be equally effective if administered in large doses, and it may be given in combination with a sulfonamide in serious infections due to this organism. The sulfonamides are considered equally as effective as the tetracyclines in the treatment of bacillary dysentery and chancroid. As a result of extensive experience in Missouri, Siniscal[7] concluded that trachoma can be best treated by sulfonamides. The sulfonamides are probably as effective as any other antibacterial agent in the management of other less common diseases, including anthrax, cholera, glanders, plague, inclusion conjunctivitis and South American blastomycosis (table 1).

The sulfonamides are generally effective in a large group of infections involving the urinary and respiratory tracts, though in some instances the

TABLE 1

Diseases in Which Sulfonamides Are as Effective as Antibiotics

Meningococcal infections
Shigella dysentery
Trachoma
South American blastomycosis
Cholera
Inclusion conjunctivitis

TABLE 2

Diseases in Which Sulfonamides Are Usually Effective

Pneumococcal pneumonia
Urinary infections due to coliform bacilli
Lymphogranuloma venereum
Streptococcal infections
Gonococcal infections
Anthrax

causative agent may be resistant to their activity (table 2). These include the common urinary tract infections due to coliform bacteria and respiratory tract infections due to pneumococci, streptococci, Hemophilus and Klebsiella. While the sulfonamides will effectively control the clinical manifestations of the hemolytic streptococcal infections as well as their suppurative complications, recent evidence indicates that they are not so valuable as penicillin in preventing the late complications of rheumatic fever and glomerulonephritis. However, once the streptococci have been eliminated from the throat the prophylactic administration of the sulfonamides will usually prevent subsequent infections.[8]

Because of the diffusibility and the additive antibacterial effect, the sulfonamides often are of definite value when used in combination with the antibiotics (table 3). The sulfonamides are as effective as any other single

TABLE 3

Diseases in Which Sulfonamides Are of Value in Combination with Antibiotics

Actinomycosis (+ penicillin or iodides)
Pneumococcal meningitis (+ penicillin)
H. influenzae infections (+ streptomycin or chloramphenicol)
Friedländer's pneumonia (+ streptomycin or tetracycline)
Brucella infections (+ streptomycin)
Plague (+ streptomycin)

agent in the treatment of infections due to the anaerobic and aerobic actinomyces, and in combination with penicillin or iodides they are probably more effective. In our experience a practical plan has been to administer both penicillin and sulfonamides in infections due to these organisms until the cultures become negative, then to maintain sulfonamide therapy on an outpatient basis for a period of one month after all sinuses have ceased draining.

The combination of the sulfonamides with penicillin in the treatment of pneumococcal meningitis is now generally accepted as being superior to the use of either agent alone. Some observers feel that the sulfonamides are definitely of value in the treatment of *Hemophilus influenzae* meningitis in combination with streptomycin or chloramphenicol.

Occasionally the sulfonamides may be effective in infections resistant to the antibiotics, such as infections due to Proteus, Pseudomonas, Salmonella, Aerobacter and other gram-negative bacilli (table 4).

During the past five years approximately 500,000 gm. of sulfonamides have been used yearly at the Jefferson Davis Hospital. Much of this drug

TABLE 4

Diseases in Which Sulfonamides Are Occasionally Very Valuable

Proteus infections
Pseudomonas infections
Salmonella infections
Staphylococcal infections

has been used as a prophylaxis against urinary tract infections while indwelling catheters were in place, for nonspecific and mixed respiratory infections, for diarrhea, urinary tract infections, preoperative and postoperative prophylaxis, and in combination with antibiotics in the management of mixed infections complicating burns and open wounds. The sulfonamides were used in many outpatients in whom an oral antibacterial agent was preferable. Sulfonamide therapy was found to be of particular value in the treatment of outpatients with pneumococcal pneumonia. Patients were routinely given injections of a long-acting penicillin, then placed on a sulfonamide by mouth, thus allowing them to be followed at four or five day intervals rather than shorter periods. During the past year five patients were admitted to the hospital who either developed empyema following pneumococcal pneumonia, or whose empyema progressed following the institution of therapy. In four of these patients procaine penicillin had been administered once daily for periods of from three to five days prior to admission, and one of the patients had received erythromycin for three days. On the other hand, none of the patients receiving the combination of penicillin and sulfonamide developed empyema.

During this period of five years of the extensive use of the soluble sulfonamides in this hospital, no examples of renal toxicity have been observed and there have been no instances of agranulocytosis or aplastic anemia traceable to sulfonamide therapy.[9] Transient leukopenia was not infrequently observed, but this was reversible in each case. Dermatitis was occasionally seen, and one case of hypoprothrombinemia was observed in a patient with meningococcal meningitis receiving sulfisoxazole and sulfadiazine. An interesting complication of sulfonamide therapy was noted in a patient seen in another hospital, who on two occasions following sulfonamide therapy developed fever, arthritis and myalgia, and typical L.E. cells were seen in the peripheral blood. The first episode subsided spontaneously, but the second was more severe and subsided more slowly after the institution of cortisone therapy.

It is quite difficult to evaluate the incidence of toxic and allergic reactions associated with drug therapy. It may be impossible on occasions to separate manifestations of the primary disease from drug toxicity. Today patients rarely receive one drug alone for more than extremely short periods, so that undesirable effects of one drug may be thought to be due to another. Once a particular toxic manifestation is found to be associated with a chemotherapeutic agent, it is often innocently incriminated. Of the patients re-

ported to have developed aplastic anemia due to Chloromycetin, almost half had never received the antibiotic. From the evidence provided in the reported literature it appears likely that toxicity to the recently developed sulfonamides is no greater than that seen in association with antibiotic therapy (table 5). During the past two years at Jefferson Davis Hospital more patients have had sufficiently severe drug reactions to require hos-

TABLE 5

Undesirable Side Effects Associated with the Administration of the Sulfonamides and the Commonly Used Antibiotics

	Newer Sulfonamides	Penicillin	Streptomycin	Tetracyclines	Chloramphenicol
Dermatitis	1.5%	1.2–7.8%	7–10%[1]	Rare 0.13[4]	Rare 0.3[4]
Blood dyscrasias					
Agranulocytosis	0.1%[3]	0			
Aplastic anemia	rare	0		rare	rare
Purpura	0.03%	rare	1%	or	(55 cases)[5]
Hemolytic anemia	0.05%	0		absent	
Hypoprothrombinemia	rare	0			
Renal toxicity					
Toxic nephritis Hematuria Anuria	rare	0	rare	0	0
Hepatitis	0.1%[3]	0	0	rare	0
Gastrointestinal toxicity					
Nausea	1%	0	rare	23%[4]	7.8%[4]
Vomiting	0.3%	0	rare	19%	5.6%
Diarrhea	rare	0	rare	12%	5.1%
Neurotoxicity	rare	rare	common	rare	rare
Superinfections	rare	1.4%	13%	10%	15%[2]
Anaphylaxis	rare	occasional 130 cases[5]	rare (5 cases)[5]	0	0
Fever	1.5%[3]	rare	uncommon	0	0

[1] Long term therapy.
[2] From Weinstein et al.
[3] Based on sulfadiazine.
Apparently less common with new sulfonamides.
[4] From Kutscher et al.
[5] From von Oettingen.

pitalization following penicillin therapy than following sulfonamide administration.

Today there is considerable interest in the increasing frequency of serious infections due to the antibiotic-resistant staphylococci and gram-negative bacilli. This increase is undoubtedly due to the wide use of the antibiotics and the selective elimination of sensitive strains. Many workers have also been quite concerned with the increasing frequency of severe superimposed

infections developing during antibiotic therapy due to these same organisms, as well as to *Candida albicans*. Weinstein, Goldfield and Chang [10] have reported that superinfections occur in 1.4% of patients receiving penicillin therapy, and in as high as 15% of patients receiving other antibiotics. The development of superimposed infections has not been a significant problem with sulfonamide therapy. This is probably due to the broad general suppressive effect of this group of drugs but the much less potent antibacterial effect of the sulfonamides as compared to the antibiotics, creating less marked changes in the normal bacterial flora. It is difficult to determine the significance of the problem of superinfection as a cause of death, but it is our impression that it is frequently an important contributing factor.

It appears as though new antibiotics will not be developed as rapidly as microörganisms adapt to growth in their presence. A possible solution to the problem of the rapidly increasing incidence of antibiotic-resistant infections is to reserve our most potent agents for serious illnesses and infections generally resistant to the sulfonamides. An exaggerated picture of the importance of the antibiotics may have been created by the fact that many of the authorities writing in the field of infectious diseases have experience primarily with problem cases and see very few of the routine infections handled in a doctor's office or in a hospital outpatient clinic. Most of the infections seen today involve either the respiratory, gastrointestinal or urinary systems, and the majority of these infections are sensitive to the sulfonamides. It has been stated that from 70% to 90% of uncomplicated urinary tract infections will respond to sulfonamide therapy.[3] The use of less potent drugs in mild infections of this type may delay the development of antibiotic-resistant strains and reserve the most effective agents for the most serious illnesses.

Finally, a point of importance to the patient, the doctor and society is the cost of therapy. The average daily cost to the patient for sulfonamide therapy is approximately 50¢, as compared to $2.00 for the tetracycline antibiotics.

Summary

The development of the more soluble sulfonamides and the sulfonamide mixtures has virtually eliminated the most frequent of the serious toxic effects of the sulfonamides—the formation of crystals in the renal tubules producing hemorrhage and obstruction.

2. The frequency of the other undesirable side effects is probably in the same range as that seen in association with antibiotic therapy.

3. The sulfonamides are less potent antibacterial agents than the antibiotics, but also produce less drastic changes in normal flora of the body and the subsequent superinfections.

4. Sulfonamides are as effective as the antibiotics in meningococcal infections, bacillary dysentery, chancroid and trachoma. They are usually

effective in most respiratory tract infections and in uncomplicated urinary tract infections.

5. The sulfonamides are of value in combination with the antibiotics in treating actinomycosis, pneumococcal meningitis, *H. influenzae* infections and Friedländer's infections.

6. The use of the sulfonamides in minor infections due to sensitive organisms may delay the development of antibiotic-resistant strains of bacteria and reserve the more potent agents for serious infections.

Summario in Interlingua

Le valor del antibioticos es hodie limitate per tres importante problemas: (1) Le crescente frequentia de sever e a vices mortal reactiones de hypersensibilitate. (2) Le disveloppamento de superinfectiones in le curso del therapia a antibioticos. (3) Le crescente frequentia de infectiones per staphylococcos resistente a antibioticos e per bacillos a Gram negative. Le disveloppamento del solvibile sulfonamidos ha practicamente eliminate le previemente plus frequente effecto toxic de iste drogas, i.e. le formation de crystallos in le tubulos renal con consequente hemorrhagia e obstruction. Le frequentia del altere regrettabile effectos lateral del sulfonamidos es probabilemente del mesme rango como le frequentia de tal effectos lateral occurrente in association con therapias a antibioticos. Ben que le sulfonamidos es minus potente agentes antibacterial que le antibioticos, illos ha le distincte avantage que illos produce alterationes minus drastic in le flora normal del corpore e in le sequente superinfectiones.

Le sulfonamidos es tanto efficace como le antibioticos in le tractamento de infectiones meningococcal, dysenteria bacillari, chancroide, e trachoma. Le sulfonamidos es usualmente efficace in le majoritate del infectiones del vias respiratori e in non complicate infectiones del vias urinari. Illos es etiam de valor, in combination con le antibioticos, in le tractamento de actinomycosis, meningitis pneumococcal, infectiones de *Hemophilus influenzae,* e pneumonia de Friedländer.

Le uso de sulfonamidos in minor infectiones causate per organismos sensibile pote retardar le disveloppamento de racias de bacterios resistente a antibioticos e assi permitte reservar le plus potente agentes, i.e. le antibioticos, pro uso in serie infectiones.

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ALLERGIC REACTIONS TO SULFONAMIDE AND ANTIBIOTIC DRUGS *

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If, indeed, the age of chemotherapy is only in its beginnings, we may certainly expect to see increasing numbers of reactions to drugs, and we can also anticipate an increasing demand for clarification of the mechanisms which underlie such reactions,—mechanisms now explained by analogy with immunologic principles for the most part established for substances other than drugs and almost exclusively in animals. The need for clarification of these problems as they arise in man warrants far more investigative effort than has been devoted to them so far.

The subject of allergy to drugs in general has been reviewed in some detail recently by three writers having somewhat different interests. The reader is referred to two reviews, both by Carr,[1, 2] and two recent books. The first of these, by Meyler,[3] is essentially a compilation, and a very useful one, of the reported reactions to drugs. The second, by Alexander,[4] includes both a discussion of mechanisms and immunologic principles as they are applied to drugs, and a very helpful account of the reactions to which various drugs may give rise.

All drugs made available for treatment of disease in man have been subjected to intensive study as regards their toxicity. Toxic reactions appear in proportion as the dosage of a drug is increased and are usually readily recognized. Because much of the preliminary data is obtained in animals, and because allergic reactions of sufficient intensity to be recognizable are uncommon in animals, the capacity of any new drug to produce allergic disease in man must await extensive clinical use, allowing opportunity for repeated exposure as well. Furthermore, the manner in which a drug is administered often changes as experience grows, and both the manner of administration and previous exposure are important factors in the development of allergic reactions (see below). For these reasons, the incidence of allergic reactions tends to grow as a drug is used more and more extensively.

Previous exposure to anti-infectious agents is becoming increasingly widespread. Not only is there an unfortunate tendency for pharmaceutical houses to market, for physicians to prescribe and for patients to use nose-drops, sprays, eyedrops, troches, chewing gum and ointments containing what are probably ineffective amounts of a sulfonamide or antibiotic, but exposure occurs from other sources as well. Polio vaccine currently available contains 200 u. of penicillin per cubic centimeter. The sulfonamides

* From the Symposium on Infection, presented at the thirty-sixth Annual Session of the American College of Physicians, Philadelphia, Pennsylvania, April 29, 1955.

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and antibiotics are widely used in animal husbandry and almost certainly reach the table of a large proportion of the population in meats, eggs, cheese and milk. A recent nationwide survey indicates that it is not unusual for randomly selected milk samples to contain 50 u. or more of penicillin per quart.[5] Whether such amounts are important as a health hazard is not now known. But who can claim *no* previous exposure to the sulfonamides or penicillin today? Allergists are especially aware of the remarkable degrees of sensitivity which develop in some patients, and many flatly refuse to carry out patch or intracutaneous tests with a drug suspected as the cause of a severe reaction for fear of aggravating the process. If this fear is justified, the small quantities referred to above may well be clinically significant.

In the matter of allergic reactions to drugs, one is faced with a kind of paradox. The best illustration is penicillin. This antibiotic was considered to be not only highly effective, but also remarkably nontoxic and relatively cheap. As a consequence it has been administered to a tremendous number of people, largely by injection. This "very safe" drug is now considered the most important cause of allergic reactions among all the anti-infectious agents, and the frequency of such reactions appears to be rising.

In view of the present unsatisfactory knowledge of mechanisms underlying allergic reactions to drugs, it does not appear profitable to review the theoretic aspects of the subject here other than to recall that allergy to a drug presupposes contact approximately five or more days before the onset of the reaction. Furthermore, the manifestations we recognize as allergic likewise presuppose interaction between the drug and an antibody formed as a consequence of contact with the drug.

Predisposing Factors

Certain conditions seem to predispose to the development of allergic reactions. Views regarding predisposition are based on clinical observation to some extent, but also very largely on animal experiments. Prolonged exposure or, perhaps more important, repeated exposure, seems to favor the development of allergic reactions. Although allergic reactions appear to be strikingly independent of quantitative factors, in a general way a large dosage of a drug is more likely to give rise to allergy than is a small dosage. Of more importance is the manner in which the drug is given. Oral administration seems to be least conducive to allergy. Abundant evidence in animals indicates that injection is usually much the most effective means of inducing antibody formation or allergy, and the same seems to apply to drugs given to man. Intramuscular, intravenous or subcutaneous injection of readily soluble preparations all may produce this result, and intramuscular injection of long-acting, slowly-adsorbed preparations causes a still greater number of reactions. A good example of this is the high incidence of reactions to penicillin in wax preparations. This clinical observation has its counterpart in those experiments in animals showing that antigens incor-

porated in an adjuvant serving to delay adsorption and at the same time promote an inflammatory reaction (by the addition of acid-fast bacilli) are remarkably active in promoting the development of antibody and allergic reactions.

If the induction of an inflammatory reaction is indeed an important factor here, then the presence of inflammation (infection, irritation from previous injections or tissue injury or necrosis) at the injection site may predispose to the development of drug allergy. The reputation for high sensitizing power which penicillin now enjoys may perhaps be explained by the fact that until recently penicillin was given almost exclusively by injection, and even now, though available in tablet form, is usually given in this way. By contrast, tetracycline and related antibiotics are usually given by mouth and perhaps for this reason produce fewer reactions. Intramuscular administration of these antibiotics on a scale comparable to penicillin might give us an entirely different impression of their sensitizing power.

A third factor is topical application, on the skin, in the eye and on other mucous membranes. Here the skin is probably much the most important, especially if it is already the seat of inflammation or an eczematous rash. For example, when used topically for the treatment of skin infections, the sulfonamides leapt into prominence as a cause of severe and occasionally fatal drug reactions.[6, 7, 8]

Although often stated, satisfactory evidence is lacking that those patients with the so-called atopic diseases (hay fever, asthma, eczema or hives) actually develop allergic reactions to drugs more often than those without them. Nevertheless, clinical experience clearly shows that when allergic reactions do occur in this group, they tend to be much more severe than in the "non-allergic." Asthma, glottal edema and vascular collapse are especially common in the atopic and account for the bulk of the acute and occasionally fatal reactions to drugs.

Types of Reactions and Their Incidence

There are abundant reports of allergic or possibly allergic reactions to drugs describing a tremendous variety of manifestations. As most of these are isolated reports, it is usually impossible to know how often many of these reactions occur. Undoubtedly those that are most striking and that are also the most serious find their way into the literature, whereas minor or apparently trivial reactions are unreported. For this reason, serious drug reactions may appear to occur more frequently than is actually the case.

It is probably safe to say that any drug can give rise to any type of allergic reaction. Fortunately, certain reactions are produced much more frequently by some drugs than by others. An attempt has been made in table 1 to indicate the relative frequency of reactions produced by the sulfonamides and antibiotics.

In those who are receiving a drug for the first time, allergic reactions

do not appear for at least five days. The onset is usually insidious and the manifestations develop slowly over a period of hours or days. Fever is probably the most common reaction. When alone, it is not usually serious, but it may create diagnostic difficulties (see below).

TABLE 1

Summary of the Allergic or Possibly Allergic Reactions to the Sulfonamides and Antibiotics with an Indication of Their Approximate Incidence

	Approximate Incidence*				Remarks
	Common	Uncommon but Significant	Rare	%	
Sulfonamides	B_1,A_1	C_1,C_2	C_3,B_4, A_6,B_5, A_3	5	Sulfathiazole and those drugs hydralized to sulfathiazole cause rashes more commonly than the others of this group, especially a type simulating erythema nodosum. Topical application can induce high degrees of allergy and is not advisable. Methyl sulfathiazole produced peripheral neuritis with relative frequency. The drugs of this group cross react in some degree both immunologically and allergically. Gantrisin seems to produce fewest allergic reactions, but this drug is the most recently introduced.
Penicillin	A_2,A_3, A_1,B_1	A_4	B_5	1–10	Probably now causing more allergic reactions than the other antiinfectious agents combined, perhaps because of very wide use. The various penicillins tend to cross react in allergic persons. The relationship between allergy to penicillin and past epidermophytosis has not been settled. Fever, malaise and lymphadenopathy occurring during treatment of primary or secondary syphilis ("Herxheimer's reaction") is not an allergic reaction to penicillin. The incidence of allergic reactions with various preparations is least with oral, greater with crystalline penicillin IM, and even greater with procaine penicillin IM. The procaine present in the last is rarely a cause of difficulty.
Streptomycin	B_1,A_1, A_5	A_2	—	10	This drug, often used for the treatment of tuberculosis, is given for long periods of time and this may explain the relatively high incidence of allergic reactions which are usually not serious. Deafness and labyrinthine involvement are not considered here. A histamine-like substance was present in early lots, causing flushing and a fall in blood pressure.

TABLE I—*Continued*

	Approximate Incidence*				Remarks
	Common	Uncommon but Significant	Rare	%	
Chlortetracycline Oxytetracycline Tetracycline	B_1,A_1	—	—	1–2	Closely related chemically, they probably cross react in allergic patients. The chief side-effects, mainly gastrointestinal and including pseudomembranous colitis, are probably not allergic.
Chloramphenicol	B_1,A_1	—	—	Low	Incidence of reactions is low, but because of the occasional occurrence of aplastic anemia, which may be fatal, the drug is used much less than the other antibiotics.
Erythromycin, Bacitracin and the Other Newer Antibiotics	B_1,A_1	C_4	—	Low	For the most part these drugs produce very few allergic reactions. However, viomycin has produced maculopapular rash, urticaria, fever and asthma.

A	B	C
Allergic	*Probably Allergic*	*Possibly Allergic*
1. Rash, usually maculopapular but variable	1. Fever alone	1. Leukopenia
2. Urticaria and angioneurotic edema	2. Purpura (often not thrombocytopenic)	2. Anemia
3. Serum disease syndrome	3. Henoch's and/or Schönlein's purpura	3. Nephritis or nephrosis
4. Acute allergic shock or acute "anaphylaxis"	4. Agranulocytosis	4. Aplastic anemia
5. Eosinophilia	5. Necrotizing angiitis (including periarteritis)	5. Acute hemolytic anemia
6. Exfoliative dermatitis	6. Migratory pulmonary infiltrations with eosinophilia†	6. Hepatitis
7. Asthma		7. Peripheral neuritis

* The letters and subscripts refer to the reactions listed under A, B and C. The letters in the table are arranged in approximate order of incidence.

† Often erroneously referred to as Löffler's syndrome.

There are scattered reports of all of the above reactions occurring during the administration of the sulfonamides and antibiotics. One may probably assume that any of these reactions *may* follow administration of any of the anti-infectious agents mentioned.

The skin reacts in a highly variable manner. The most common rashes are either simple erythema or erythema and papules. The nature of the rash is determined by the particular drug given in only a few instances. Sulfathiazole is especially prone to give rise to a rash resembling erythema nodosum, although the lesions are usually smaller and more superficial than those occurring spontaneously. Succinylsulfathiazole (Sulfasuxidine) and phthalylsulfathiazole are hydralized to sulfathiazole and may therefore cause

identical reactions. Penicillin has a strong tendency to cause urticaria, rarely caused by other drugs. A syndrome which includes urticaria as a rule, likewise usually caused by penicillin and only rarely by other drugs, closely resembles serum disease. Rashes other than urticaria may be associated with this syndrome, and erythema marginatum or erythema multiforme with bullous lesions is occasionally seen. Purpura, with or without thrombocytopenia, but usually associated with so-called "capillary fragility," * demonstrable by the tourniquet test, is probably again most often caused by penicillin. Such reactions might, under exceptional conditions, be confused with purpura associated with sepsis, especially meningococcal. Exfoliative dermatitis is an infrequent reaction which may be caused by any drug. It is usually severe and is potentially dangerous.

Albuminuria with or without white cells in the urine may occur, apparently as an allergic reaction to the sulfonamide drugs. Hematuria during administration of these drugs may be attributable to irritation from precipitated crystals of drug in the renal tubules. However, in the absence of known intrinsic renal disease, hematuria associated with albuminuria with or without white cells is potentially serious and therapy should be stopped. Oliguria or anuria may occur as well.

Leukopenia may develop after sulfapyridine, sulfathiazole, sulfadiazine and, less often, after the other sulfonamide drugs have been administered for two to three weeks or more. This may not be an allergic reaction, and it is usually not serious. Agranulocytosis is occasionally caused by the sulfonamide drugs, and only very sporadically by antibiotics. This may indeed be an allergic reaction, it is potentially fatal, and the responsible drug should be withheld. Moderate degrees of anemia are seen during therapy with the sulfonamides, but uncommonly with the antibiotics. Occasionally chloramphenicol causes aplastic anemia which may be fatal. This reaction usually occurs after prolonged or repeated use. It is not known whether this reaction is allergic. Sulfanilamide and, rarely, other sulfonamide drugs may cause acute hemolytic anemia, a reaction which may occur promptly on what appears to be initial contact with the drug and which probably is not allergic in nature.

Widespread and often very serious reactions to drugs may manifest themselves as diffuse involvement of the vascular system. Such reactions are often referred to as periarteritis nodosa, but in many instances they show important differences. Grouping all such reactions under the term necrotizing angiitis, Zeek et al.[9, 10] suggest that this type of allergic reaction be designated as allergic granulomatous angiitis. The distinction has practical importance in the interpretation of tissue biopsies.

Other reactions may involve the liver, producing jaundice, or the nervous system. The role of an allergic mechanism in such reactions is obscure.

* According to studies in the hamster cheekpouch by Dr. Breuton R. Lutz and his associates, the lesion probably is not, strictly speaking, in the capillary, but at the point where the capillary and venule join.

Allergic manifestations may group themselves together to form syndromes. The "serum disease" syndrome has already been mentioned. The combination of fever, rash and mucous membrane lesions, often referred to as erythema multiforme exudativum, occasionally appears as a reaction to drugs, probably more often to penicillin than to others. As the first of these may also occur as a reaction to antiserum given for prophylaxis or treatment of an infection treated with an anti-infectious drug, and as the second may occur in the course of nonbacterial pneumonia, possibly ornithosis,[11] confusion may easily arise.

Reactions in Those Already Allergic

There is no way of knowing whether a patient who has had an allergic reaction to a drug will react again on re-administration. It is safest to assume that he will. If a reaction does occur, it tends to appear promptly. Such accelerated reactions may occur even though there was no reaction during the first course of therapy. In such instances, the allergic state presumably developed after treatment was stopped and therefore never became manifest.

Accelerated reactions usually are similar to those seen on first administration of a drug, but the manifestations tend to be more striking. With penicillin in particular, but only rarely in the case of other antibiotics or the sulfonamides, a violent reaction may appear within a few seconds or minutes. Such reactions usually include urticaria, angioneurotic edema, dyspnea with asthma and vascular collapse, and may be fatal.

Recognition of Allergic Reactions in the Course of Infectious Diseases

The problems presented by an allergic reaction to a drug occurring during the course of an infection can indeed be confusing. One of the most common is fever, which is usually recognized by its persistence in the face of recovery from the infection as judged by improvement in the patient's subjective state of well being, clearing of physical signs, a fall in pulse, disappearance of leukocytosis and a decrease or disappearance of the infecting organism from the sputum, throat, nose, urine or other location. Fever caused by a drug usually subsides in 24 to 36 hours after administration is stopped. Accurate diagnosis, including careful identification of the infecting organism whenever possible, and careful appraisal of the patient's course, will decrease the instances wherein drug fever creates a serious problem.

Though occasionally confusing, the appearance of a drug rash will usually be promptly recognized as such. More difficult is the fortunately much less common involvement of the vascular, renal, hepatic or blood-forming systems. Where the infection itself it not a likely cause, it is best not to temporize but to incriminate allergy to one or more drugs being administered

and to stop therapy with these agents at once. Biopsy of the bone marrow or of the skin and muscle may be helpful.

In patients who are very acutely ill, it is uncommon to recognize allergic reactions to drugs. This may be simply a matter of the overwhelming dominance of the manifestations of the infection which obscures the drug reaction. On the other hand, two factors may militate against the occurrence of drug reactions in acutely ill patients. In the first place, strong physiologic insults, of which a severe infection would be one example, tend to induce a state of tissue unresponsiveness to allergenic stimuli. In the second place, though possibly related to or even part of the first, acute infections may induce increased activity of the adrenal cortex, resulting in sufficient endogenous production of steroids to suppress allergic reactions.

The Value of Skin Tests

Skin tests have a very limited application in the diagnosis of allergic reactions to anti-infectious drugs. Scratch or intracutaneous tests are usually entirely negative in persons who have or have had reactions fulfilling the usual criteria for allergy. In those who have developed allergy to a drug through topical application to the skin, the skin will often react on contact and here the patch test is applicable. However, in the course of treating infectious disease, such is not often the case, and furthermore, patients who react to a drug by patch test may have a serious systemic reaction as well, which may take the form of exfoliative dermatitis. Even here the scratch or intracutaneous test is usually negative.

Serum obtained from normal persons receiving the usual dosage of a drug for three to four days has been substituted for the drug alone in intracutaneous tests, and a good correlation was claimed between reactions in the skin and the presence of allergy to the sulfonamide drugs.[12] Attempts to confirm this have been unsuccessful. Tests done with serum mixtures are notoriously difficult to interpret.

The most striking success, if success is indeed the right word, in the application of skin testing to the problem of allergic reactions to anti-infectious agents has been obtained with penicillin. Erythema, whealing and itching developing within 20 minutes can often, but not always, be elicited upon intracutaneous injection of penicillin into those with urticaria or the serum disease syndrome. Skin sensitizing (or passive transfer) antibody may be present in the blood. In some patients no immediate reaction develops, but an erythematous indurated papule appears in 24 to 48 hours. The significance of such delayed skin reactions is not entirely clear, but those having them do appear to have a high incidence of allergic reactions to penicillin.

We have studied one patient who, several months following an acute systemic reaction, accompanied by asthma, to the intramuscular injection of procaine penicillin, exhibited a delayed reaction on skin test. Inhalation of aerosolized penicillin from a nebulizer was followed by a prompt fall in

vital capacity and the development of asthmatic signs. When tested again by skin test four months later, an immediate type of skin reaction occurred, no reaction being visible after 48 hours.[13] Upon retesting again several months later, the skin reaction had reverted to the delayed type and pulmonary reactivity to penicillin was no longer demonstrable. (These most recent tests have not been reported.) These findings indicate a significant relationship in this patient between the immediate and the delayed skin reaction and pulmonary sensitivity to penicillin. The practical value of such procedures must await much more extensive investigation.

Treatment

Unless the manifestations are very mild, or unless the indications for continued treatment are very strong, administration of a drug which has produced an allergic reaction should be stopped at once. Elimination of a drug is facilitated by administration of fluids and maintenance of a urinary output greater than 1,500 c.c. in 24 hours. Most drug reactions require no other treatment. To be sure, many drug reactions are not serious and some are only temporary, disappearing completely in a few days, even in the face of continued administration of the offending drug. Such cannot be foreseen, however, and as any drug reaction may progress to involve many systems and terminate fatally, continued administration is contraindicated.

Most drug reactions, especially fever and rashes, clear within 24 to 36 hours after administration is stopped, but there are notable exceptions. Urticaria caused by penicillin may persist for weeks, months and possibly a year or more, and exfoliative dermatitis may require weeks to clear. Reactions characterized by a necrotizing angiitis may progress after the drug is stopped and terminate fatally. The same is true of aplastic anemia caused by chloramphenicol, and occasionally agranulocytosis caused by the sulfonamides and possibly by antibiotic drugs as well.

Some drug reactions require special measures. Acute reactions developing usually within a few minutes after administration (often parenteral) are characterized by urticaria or angioneurotic edema, asthma or glottal edema and vasomotor collapse. Such reactions require immediate measures to maintain the blood pressure and an adequate airway. Epinephrine, 1:1000 in a dose of 0.5 c.c. given subcutaneously, will have both these effects and is the most effective single measure. The prompt intravenous administration of an antihistaminic drug will help to allay allergic manifestations and will act synergistically with epinephrine to maintain the blood pressure. For a more prolonged pressor effect, arterenol given as a slow intravenous infusion is useful, and again the effect will be enhanced if an antihistaminic drug is also given. Epinephrine, 1:100, or isopropylarterenol (Isuprel), 1:100 or 1:200, given as an aerosol from a good nebulizer by inhalation, will help to relieve asthma if present. Oxygen will relieve

hypoxia, if present, but helium and oxygen mixtures are probably ineffective.[14]

The initial injection in a course of drug therapy is the one most likely to give acute reactions of this type. If this injection is given into an extremity rather than into the buttocks, measures can then be taken to delay absorption by: (1) placing a tourniquet proximal to the site; (2) placing ice or any ice-cold object on the site; and (3) injecting 0.1 or 0.2 c.c. of epinephrine, 1:1000, into the site. Little or no help can be expected from ACTH or adrenocorticosteroids in these reactions, as the crucial phase is usually past by the time these measures would have an effect. Furthermore, these acute reactions will probably still occur in those receiving such therapy, as the observable induced skin and pulmonary reactions to allergens are little influenced thereby.[15-18]

Although the very acute manifestations of drug allergy are not treatable with ACTH or the adrenocorticosteroids, most other allergic or apparently allergic reactions respond to these measures with the disappearance of most or all of the manifestations. These may return, however, when therapy is stopped, suggesting that the effect has been suppressive rather than curative, and further suggesting that the underlying process may actually continue during treatment even though overt manifestations are lacking. For these reasons, because we are still unclear as to precisely how these agents act, and because the infectious process may be enhanced, such therapy should probably be reserved for those patients with very severe discomfort unrelieved by other measures, or for those in whom the reaction appears to be progressive and to threaten life or the integrity of vital systems. In the face of the last, such therapy may be indicated even in the presence of persisting infection which will require carefully planned treatment with an antiinfectious agent immunologically unrelated to the drug which gave rise to the reaction.

Summary and Conclusions

The frequency and potential danger of reactions to the sulfonamides and antibiotic drugs warrant the following precautionary measures:

1. Incidental and unnecessary exposure to the sulfonamide and antibiotic drugs should be held to a minimum.

2. Drugs effective and relatively safe when given parenterally should not be administered topically as ointments, nosedrops, etc. Other antibacterial agents which cannot be given systematically are available for such purposes.

3. Whenever possible, measures permitting an accurate bacteriologic diagnosis should be taken before treatment is started. Knowledge of the infecting organism will help in recognizing the cause of symptoms which persist in spite of treatment.

4. The number of drugs administered simultaneously should be held to a minimum.

5. The initial injection of a drug should be given in an extremity rather than in the buttocks, so that measures can be taken to delay absorption if a reaction occurs. This is especially important in those who have had reactions in the past and those who are to receive penicillin. Preparations suitable for treating acute allergic reactions should be available.

6. The inadvertent injection of a drug intravenously is undesirable and can be avoided by withdrawing the plunger of the syringe for a few seconds after the needle is inserted. If blood appears in the hub of the syringe, the needle should be re-inserted.

7. To those who have had allergic reactions to a drug in the past or who are believed to be prone to develop reactions, give short-acting rather than long-acting preparations.

8. Wherever possible, give sulfonamides and antibiotics by mouth.

Summario in Interlingua

Reactiones a drogas, jam frequente, va sin dubita devenir plus frequente al futuro. Assi il non es surprendente que extense revistas de iste thema ha essite publicate in le curso del passate 3 annos. Sulfonamidos e antibioticos es specialmente importante. Illos es frequentemente administrate plure vices al mesme individuo, e lor crescente usos in le campo del elevage de bestial causa lor presentia in nondum determinate quantitates in carne, lacte, e ovos. Proque illos ha le capacitate de provocar intense reactiones in certe personas illos possede un interesse special pro le studentes del plus in plus seriose problema del allergia a drogas medical.

Si nos vole administrar iste remarcabilemente utile drogas sin currer gravissime riscos nos debe familiarisar nos con le varie manifestationes del reactiones mentionate. Omne effortios deberea esser facite pro evitar expositiones innecessari e pro administrar iste drogas in le maniera que es le minus apte a disveloppar allergias. In relation a iste ultime aspecto del problema nos possede hodie un considerabile fundo de information tanto experimental como etiam clinic. Es formulate le opinion que le antibioticos del gruppo de tetracyclina con lor large spectro de efficacia attingerea possibilemente un capacitate allergenic non inferior al capacitate allergenic de penicillina si ille antibioticos esseva administrate per injectiones tanto frequentemente como penicillina.

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SERUM GLUTAMIC OXALACETIC TRANSAMINASE ACTIVITY AS AN INDEX OF LIVER CELL INJURY: A PRELIMINARY REPORT*†

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Introduction

Glutamic oxalacetic transaminase is widely distributed in animal tissues. Its greatest concentration, however, is in heart muscle, skeletal muscle, brain, liver and kidney, in decreasing order.[1] We have already shown that, when measured in serum, this enzyme is elevated after acute myocardial infarction.[2] This finding led us to study its concentration in liver diseases, since the enzyme is present in relatively high concentration in liver.

Glutamic oxalacetic transaminase is present in all human sera and will henceforth be referred to as SGO-T. Comparable concentrations are found whether chromatographic or spectrophotometric methods are employed.[3] When serum is added to excesses of aspartic acid and alpha ketoglutaric acid buffered at optimal pH in the presence of coenzyme 1 ($DPNH_2$) and malic dehydrogenase, SGO-T can be measured in a spectrophotometer by the decrease in optical density resulting from the oxidation of $DPNH_2$ to DPN (figure 1). One unit of SGO-T activity represents a change in optical density of 0.001/ml./min. at wave lengths of 340 mu. All tests done in this series of patients were performed with 0.5 ml. or 0.2 ml. of serum.

The range of SGO-T in normal adult individuals was ascertained by random and serial determinations on the sera of 500 persons without regard to the fasting state. The mean value of the normal range (5 to 40 units) was found to be 22.1 units, with a standard deviation of $\pm$ 6.8 units.

The studies following myocardial infarctions indicate that the enzyme is liberated into the blood stream following injury to the cell.[4] If the enzyme is also released from damaged liver cells, the SGO-T level should provide an index of liver cell destruction. The level and persistence of increased activity might then provide an index of active liver cell disease.[5]

SGO-T has not been found to be increased in patients with infectious, neoplastic, degenerative, metastatic, reactive, allergic or congenital disease states unless evidence of acute damage to liver tissue, heart muscle or skeletal muscle has been evident. Patients with pneumonia, active pulmonary

* Received for publication April 13, 1955.

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† Supported in part by a grant from the National Institutes of Health.

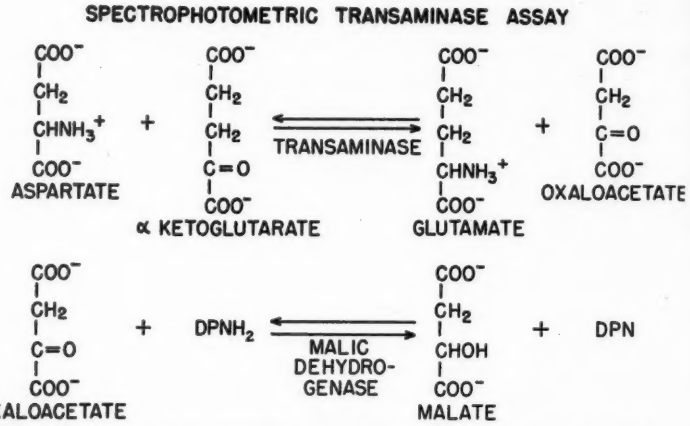

FIG. 1. Summary of the chemical reactions involved in the spectrophotometric assay of SGO-T.

tuberculosis, infections of the genitourinary tract, empyema and other infections have had SGO-T levels within normal limits. Many patients with neoplastic disease of many varieties have had normal levels of SGO-T in the presence of widespread metastases when the liver is not involved. The disease states in which the SGO-T has been followed over a period of time and found to be within normal limits are listed in table 1.

The purpose of this paper is to report the variation in SGO-T activity following acute liver cell destruction, such as that seen after carbon tetrachloride (CCl_4) poisoning in man and animals, and its activity during the course of acute infectious and homologous serum jaundice; and to compare

TABLE 1

Diseases in Which the SGO-T Has Been Found to Be Within Normal Limits in the Absence of Damage to the Liver, Heart or Skeletal Muscle

Infectious	Allergic	Reactive
Pneumonia	Hay fever	Rheumatoid arthritis
Tuberculosis	Asthma	Rheumatic fever without carditis
Cystitis	Urticaria	Chorea
Pyelonephritis	Allergic dermatitis	Lupus erythematosus
Wound infection		Polyarteritis nodosum
Empyema	*Degenerative*	
Acute cholecystitis	Cerebral arteriosclerosis	*Congenital*
Pancreatitis	Cerebral thrombosis	Congenital heart disease
Pericarditis	Cerebral hemorrhage	
Thrombophlebitis	Multiple sclerosis	*Metabolic*
	Muscular dystrophies	Hypothyroidism or hyperthyroidism
Neoplastic	Nephrosclerosis	Addison's disease
Carcinoma	Osteoporosis	Panhypopituitarism
Melanomas	Osteoarthritis	Uremia
Osteogenic sarcomas		Uremic pericarditis
Lymphomas		
Teratomas		

the levels noted in these disorders with SGO-T activity in patients with cirrhosis of varying degree, with obstructive jaundice and with metastatic carcinoma of the liver. We were interested in finding out whether the degree of SGO-T elevation is related to the amount of liver cell destruction; whether the enzyme concentration will help differentiate medical from surgical jaundice; whether SGO-T activity in chronic liver disorders indicates active liver cell destruction; whether the height and length of elevation bear any relation to prognosis; what correlation there may be between the SGO-T activity and the various tests of liver dysfunction; and whether changes in SGO-T reflect the presence of liver metastases.

Method and Material

SGO-T activity was determined spectrophotometrically on serum stored for from a few minutes to seven days at 0° C.[3] Patients with CCl_4 poisoning, acute infectious and homologous serum hepatitis, cirrhosis, obstructive jaundice, and metastatic and primary carcinoma of the liver had blood withdrawn at varying intervals during their illness. SGO-T levels as well as determinations of serum bilirubin, cephalin flocculation, thymol turbidity, A/G ratio, alkaline phosphatase, cholesterol and esters, Bromsulphalein retention and prothrombin time were done.

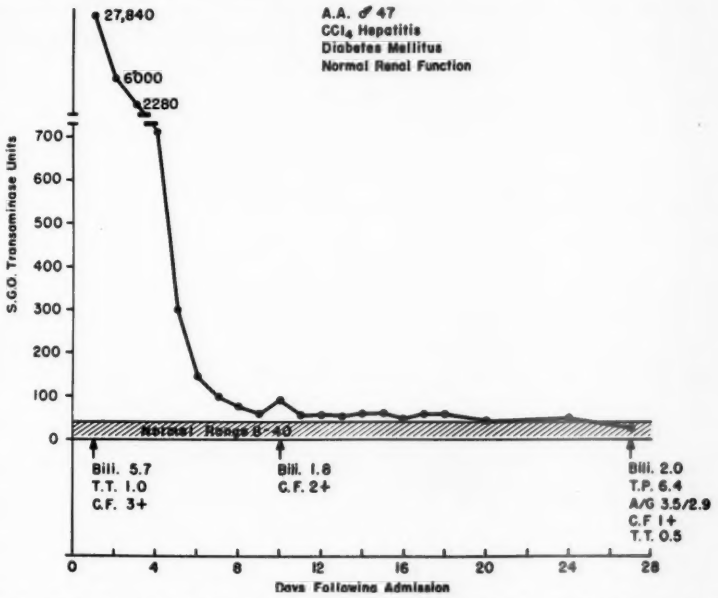

Fig. 2. SGO-T activity following CCl_4 poisoning, together with the results of some of the usual liver function tests.

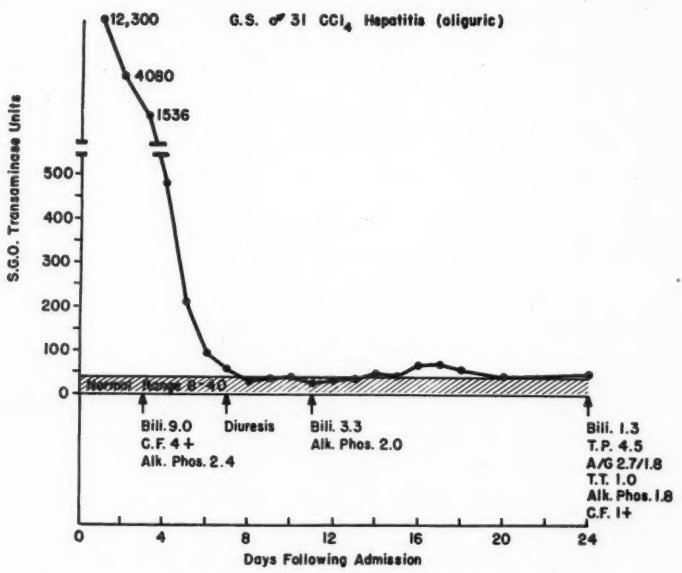

FIG. 3. SGO-T activity after CCl_4 poisoning in G. S. who, contrary to A. A. in figure 2, was oliguric. Both curves are similar.

ACUTE LIVER CELL DESTRUCTION (TOXIC)

Two patients had been exposed to CCl_4 fumes two days prior to admission to the hospital. They complained of nausea, vomiting, headache and generalized malaise. Both were moderately icteric and presented with minimal enlargement of the liver. Their course is summarized in figures 2 and 3. The tremendous elevation of the SGO-T transaminase to 27,840 and 12,340 units respectively 48 hours after exposure was striking; the enzyme activity then rapidly fell to normal within one week. The bilirubin rose to 5.7 and 9.0 mg., respectively, and the cephalin flocculation, originally abnormal, fell to 1 plus at the time of discharge. Both patients recovered.

HOMOLOGOUS SERUM HEPATITIS AND INFECTIOUS HEPATITIS

Ten patients had homologous serum hepatitis, in six apparently transmitted during various injections and in four following transfusions. Anorexia, nausea, emesis, pruritus, dark urine and, in some instances, light-colored stools were the symptoms proffered by these patients. All had hepatomegaly and jaundice of varying degree; in two the spleen was palpable. Hospital admission was within 10 days of the onset of illness in three patients, and after 20 to 30 symptom days in the remainder. Figure 4

represents the course of illness in N. P., a 32 year old physician admitted to the hospital after one week complaining of generalized malaise of one week's duration. On the second hospital day his SGO-T was 2,140, falling gradually within 20 days to normal. All liver function tests were abnormal on the day of admission, three remaining abnormal for 40 or more days, with persistent elevation of the bilirubin to 3.0 mg. more than two months

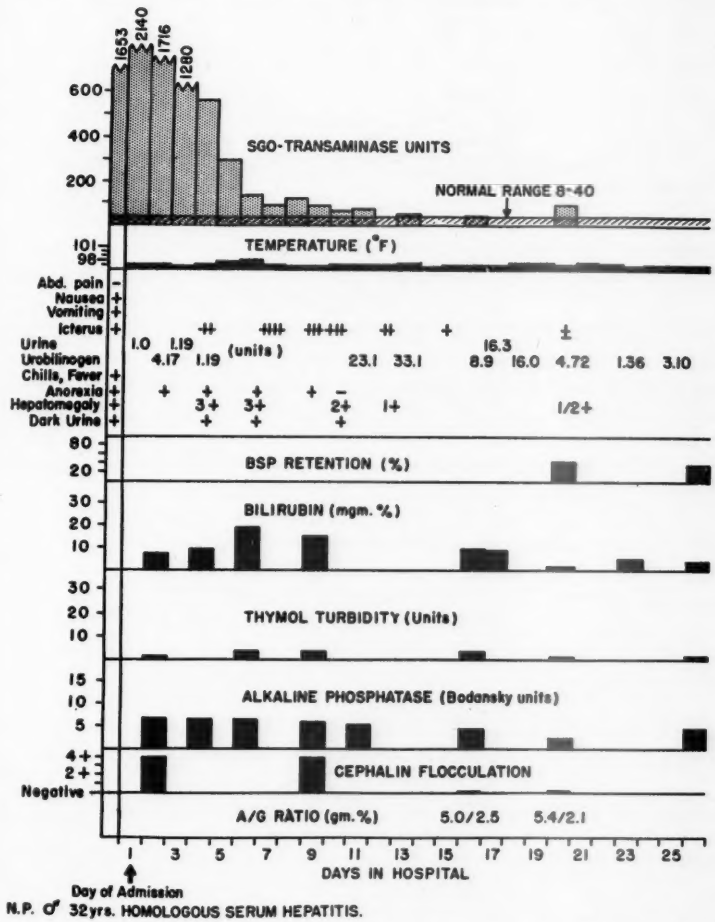

FIG. 4. Summary of the SGO-T activity, together with the values for urinary urobilinogen (Ehrlich units), blood bilirubin, thymol turbidity, alkaline phosphatase, cephalin flocculation, A/G ratio and Bromsulphalein excretion over a 26 day period in a patient with acute homologous serum hepatitis.

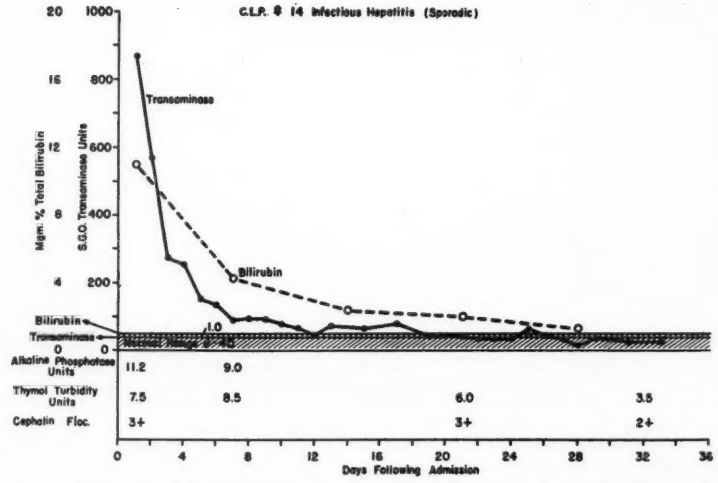

FIG. 5. SGO-T activity and bilirubin, thymol turbidity and cephalin flocculation over a 36 day period in a patient with infectious hepatitis.

later. When he left the hospital he did not rest, as suggested, and his SGO-T promptly rose to 98 units, returning to normal after two additional weeks of bed-rest.

In five of these patients the usual liver function tests remained abnormal for from 10 days to three months longer than it took for the SGO-T to return to normal limits. Three patients had levels of 2,000 or more units, four of 750 to 1,500 units, and in the remaining the level taken after 10 or more days of illness was 220 units, 176 units and 76 units. Two patients died. In one the SGO-T activity remained at 250 units during the five months of her illness. The second died on the one hundred fiftieth day of her illness of hepatic failure complicated by cardiac decompensation. The SGO-T fell from 1,245 to 50 units on the thirty-eighth hospital day, only to rise to 921 eight days before death.

Five patients had infectious hepatitis, and in four symptoms were present for one week prior to hospitalization, the fifth having been ill for five weeks.* The symptoms consisted of anorexia, nausea, vomiting and generalized malaise. All of the patients were jaundiced; three had moderate enlargement of the liver; none had splenomegaly. In three patients the SGO-T was 800 or more units on admission; in the fourth the level was 564 during the sixth week of the illness, and in the last the level was 60 on the twenty-third day of his sickness. Figures 5 and 6 represent the course of the disease which was typical for this group. In four patients the SGO-T had

* None of these patients had received injections or been given transfusions or had any contact with fresh human blood for at least one year prior to their present illness.

fallen to normal by the fourth week, and in the patient admitted during the fifth week of his illness the SGO-T had dropped to normal on the nineteenth hospital day. The tests of liver function, grossly abnormal on admission, were still far from normal at the time the SGO-T had fallen to 40 units in four of the five patients. All patients recovered and will be restudied at a later date.

Cirrhosis

Twenty-eight patients with cirrhosis of the liver (19 proved by biopsy) were studied. In eight the level of SGO-T was within normal limits; in 14 the activity was 41 to 100 units, and in six the level was more than 100 units. Table 2 indicates the percentile incidence of hepatomegaly, splenomegaly, ascites and abnormal liver function tests in the three groups. This can be stated another way by noting that in two of the eight patients with normal SGO-T activity two of the conventional liver function tests were abnormal; two had more than two abnormal tests, and four had only an abnormal cephalin flocculation test. In patients with SGO-T between 41 and 100 units three had only one abnormal test of liver function, four had two, and seven had more than two tests indicating liver dysfunction. All the six patients with SGO-T levels of 101 to 1,600 units had two or more abnormal tests of liver function. Of the last group, three patients had biliary cirrhosis.

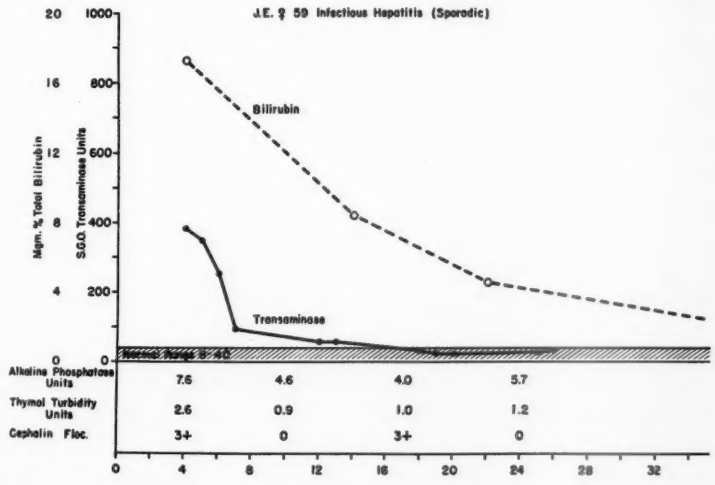

Fig. 6. Comparison of the SGO-T activity with the bilirubin, alkaline phosphatase, thymol turbidity and cephalin flocculation. Note the persistent elevation of the serum bilirubin and cephalin flocculation when the SGO-T was within normal limits.

TABLE 2

Comparison of the Incidence in Per cent of Hepatosplenomegaly, Ascites and Abnormal Liver Function Tests in 28 Patients with Cirrhoses According to the SGO-T Activity

SGO-T Units	Enlarged Liver	Palpable Spleen	Ascites Present	Abnormal						
				Bili-rubin	Cephalin Flocc.	Thymol Turbidity	BSP	Total Protein	Albu-min	Alkaline Phospha-tase
40 or less (8 patients)	50	25	63	17	100	76	67	0	13	67
41 to 100 (14 patients)	50	14	43	77	90	93	80	0	23	33
Greater than 100 (6 patients)	67	17	67	83	100	100	100	0	33	100

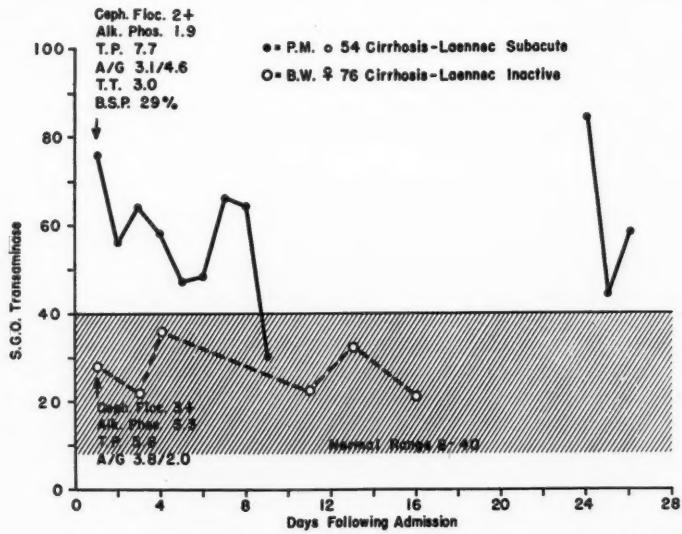

FIG. 7. Comparison of the SGO-T activity and the liver functions of two patients with Laennec's cirrhosis. See text for discussion.

Figure 7 shows the level of SGO-T in two patients with Laennec's cirrhosis—one who was asymptomatic (B. W.), and another (P. M.) who was admitted to the hospital with increasing jaundice, anorexia, nausea and generalized malaise which cleared after adequate bed-rest. Of interest in these patients was the fact that one was obviously sick with active liver disease and the other was asymptomatic. It appeared that the SGO-T level in Case P. M. may have represented active liver cell injury.

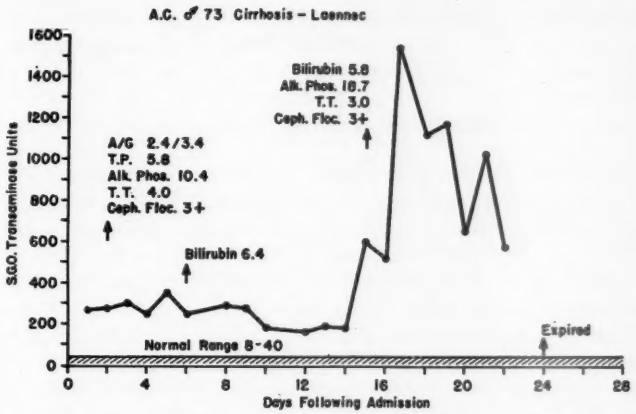

FIG. 8. This figure demonstrates the persistently abnormal levels of SGO-T in a patient with cirrhosis of the liver who died on the 24th hospital day.

Figure 8 also demonstrates this dissociation between values of the conventional liver function tests and the SGO-T in a patient with Laennec's cirrhosis who, while chronically ill the first two weeks of his hospitalization, became acutely and critically ill from the fourteenth to the twenty-fourth day, when he died. During this period the SGO-T rose precipitously. Autopsy revealed Laennec's cirrhosis with superimposed acute hepatitis.

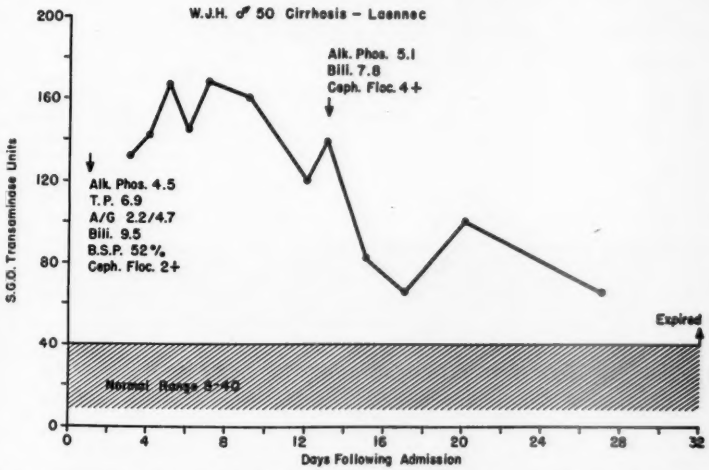

FIG. 9. Decreasing but persistently abnormal SGO-T activity in a patient with Laennec's cirrhosis who died on the 32nd hospital day.

Figure 9 shows the course of another patient with Laennec's cirrhosis who died in liver coma after a slowly downhill illness of three months' duration. Autopsy showed Laennec's cirrhosis.

Metastatic Carcinoma of the Liver

Twenty of 22 patients with proved metastatic involvement of the liver from various types of carcinoma showed increased SGO-T activity on one or more determinations. The usual liver function tests were run concomitantly, and it is interesting that in seven patients increased SGO-T activity, with levels varying from 46 to 140 units, was the only sign of liver involvement. In 13 patients the SGO-T varied from 60 to 230 units, but the alkaline phosphatase and, at times, other liver function tests were also abnormal. In two instances with small areas of metastasis both the SGO-T and all other liver function tests were normal. The level of the SGO-T elevation did not correlate with the levels of the bilirubin, alkaline phosphatase, A/G ratio, Bromsulphalein, cholesterol and esters, or any other laboratory study. It is also of interest that 20 patients who had moderate

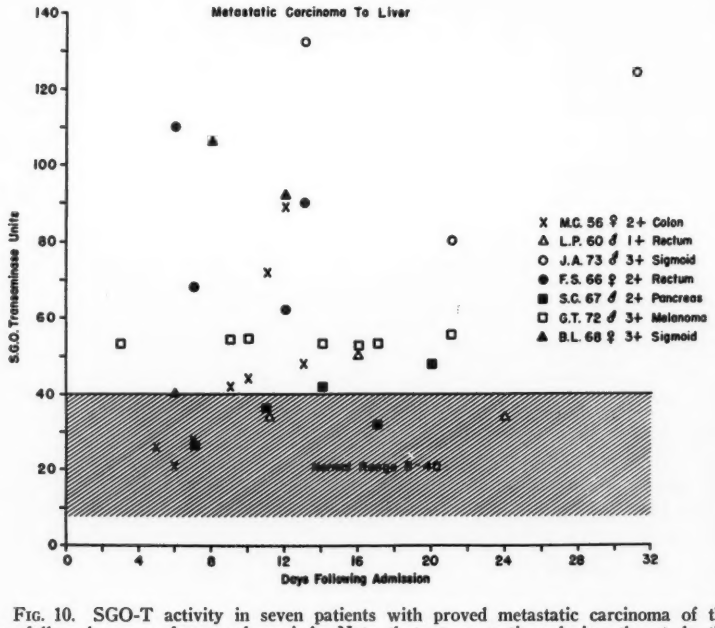

Fig. 10. SGO-T activity in seven patients with proved metastatic carcinoma of the liver followed over a four week period. Note that at some time during the study the SGO-T activity was elevated in all the patients.

to marked elevation of the alkaline phosphatase secondary to bone metastases in the absence of hepatic dysfunction all had normal SGO-T activity.

The variable level of SGO-T activity in seven patients with metastatic carcinoma of the liver is shown in figure 10. If similar symbols are connected it will be seen that at some time during the hospital study the SGO-T was elevated.

Figure 11 shows the SGO-T levels in a patient with proved primary hepatoma whose bilirubin was 5.2 mg. %, alkaline phosphatase 8.3 Bodansky units, and cephalin flocculation 2 plus. Persistent evidence of liver cell destruction was again noted and confirmed at autopsy.

It was interesting to study the enzyme alterations in a female with metastatic disease involving most of the right lobe of the liver which was resected. Preoperative levels were 60 to 80 units, but rose to 200 after resection of the right lobe of the liver and fell to normal with recovery of the patient four weeks later.

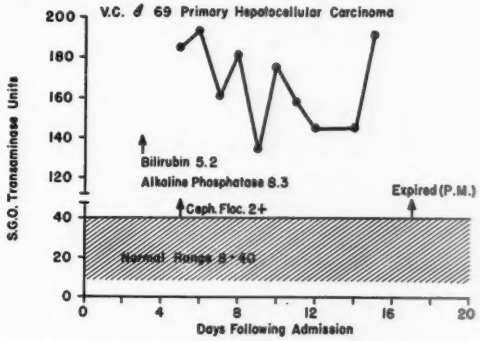

FIG. 11. SGO-T activity in a patient with primary liver carcinoma who died on the 17th day. See text for discussion.

OBSTRUCTIVE JAUNDICE

Five patients with obstructive jaundice were studied. Four had proved cancer of the pancreas, with jaundice of from two weeks' to three months' duration. In two the SGO-T activity was 120 units preoperatively, falling to normal in 14 days in one and in less than 10 days in the other. Figure 12 shows the SGO-T levels together with values for the bilirubin, thymol turbidity, cephalin flocculation, alkaline phosphatase and A/G ratio preoperatively and postoperatively in one patient with cancer of the pancreas. The second patient had a similar course. Note the lack of correlation between the SGO-T and other laboratory studies. The third had inoperable disease with liver metastases, and his SGO-T has varied between 60 and 80 units for six weeks, his bilirubin from 20 to 30 mg., and his alkaline phosphatase 20 to 45 units during the period of observation. The cephalin

flocculation and thymol turbidity stayed within normal limits. The fourth had a normal SGO-T despite obstructive jaundice of four weeks' duration.

The single patient with jaundice due to common duct stones had a preoperative SGO-T of 70 units, which fell to normal two days postoperatively after the insertion of a T tube into the common duct (figure 13). This is as rapid a return to normal as one could expect, since following any operative procedure in which muscle is cut or damaged the SGO-T usually remains elevated for one to four days.*

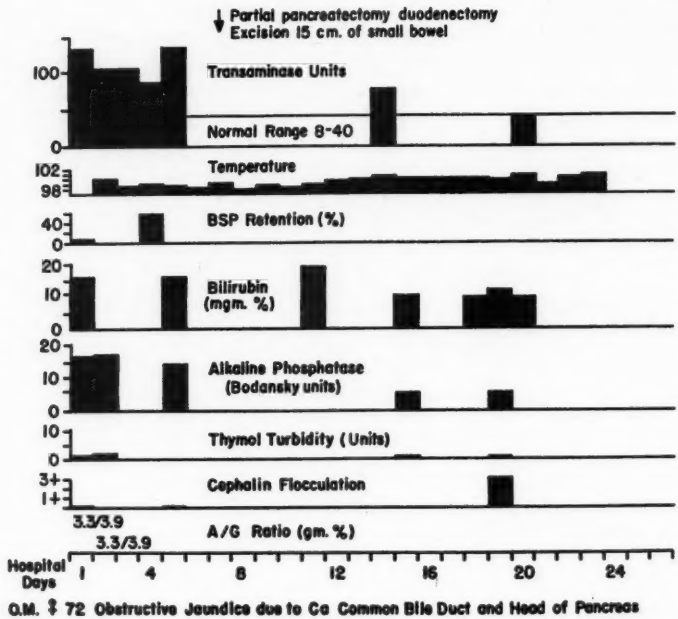

FIG. 12. Variations in SGO-T activity in a patient with obstructive jaundice due to carcinoma of the common bile duct and head of the pancreas, relieved by partial pancreatectomy and duodenectomy.

DISCUSSION

The clinical data reported here are too meager to permit any conclusions relative to the correlation, if any, between the height of the SGO-T elevation and the amount of liver cell damage. However, in collaboration with Dr. David Molander, graded damage of liver tissue was produced in rats by giving them carbon tetrachloride, 0.3 c.c./dose.[6] Figure 14 shows that

* Unpublished data.

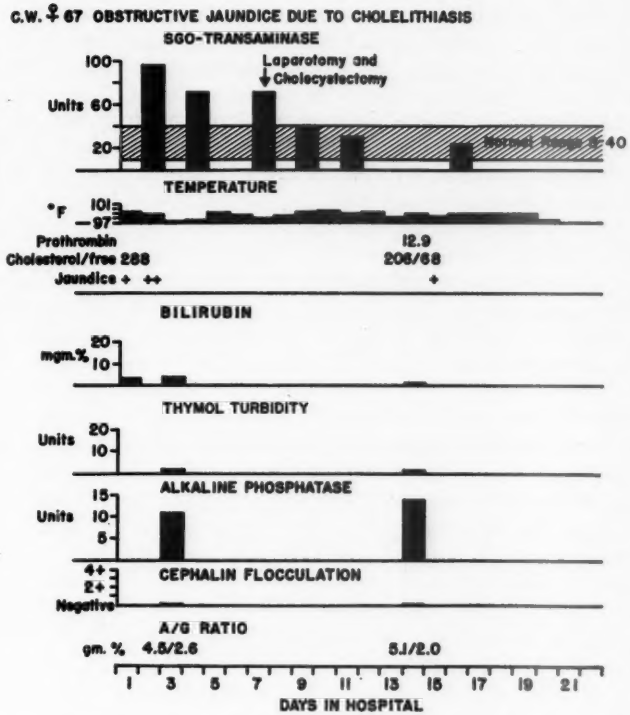

FIG. 13. SGO-T levels in a patient with obstructive jaundice due to cholelithiasis preoperatively and postoperatively.

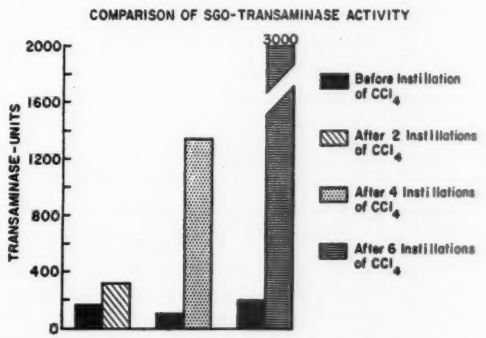

FIG. 14. Comparison of the SGO-T activity in three groups of rats intubated with 0.3 c.c. of carbon tetrachloride. One group received two instillations, the second four and the third six.

there is a close parallel between the amount of CCl_4 given to the rats and the level of the SGO-T elevation. It was our impression from the clinical course that there was a rough relationship between the severity of infectious and homologous serum hepatitis and the SGO-T activity.

Serum glutamic oxalacetic transaminase levels of from 600 to 22,500 units, with a falling titer over a period of from five to 10 days, were seen in hepatitis and acute liver cell damage due to CCl_4. In the few instances of obstructive jaundice that we have studied the SGO-T activity was not above 300 units and remained relatively constant, or increased slowly until the mechanical obstruction was relieved (figures 12 and 13). It thus appears that infectious or homologous serum jaundice can be differentiated from obstructive jaundice if SGO-T activity is measured early and serially in the course of the disease. Patients with cirrhosis or with metastases to the liver, however, cannot be separated from obstructive jaundice due to stone, cancer or other cause by study of the SGO-T activity alone.

Too few patients with cirrhosis have been followed over any period of time to state whether changes in SGO-T activity with time are common, or what might be their significance. Secondary rises in two patients with superimposed hepatitis, however, preceded rapid liver decompensation and death. Persistent elevation of SGO-T activity has been associated with a poor prognosis in the patients we have had an opportunity to observe (figure 9).

The SGO-T activity does not alter in the same direction, magnitude or time as any of the currently employed liver function tests. This has been emphasized in the presentation of the data on patients with acute toxic cell damage, in those with hepatitis and in those with cirrhosis or metastatic carcinoma of the liver. There was no correlation between the SGO-T activity and the erythrocyte sedimentation rate, white blood count, temperature, C-reactive protein or antistreptolysin titers in patients with various infectious diseases whose SGO-T activity has been studied, or in our patients with liver disease. Changes in the level of SGO-T, therefore, cannot be considered as those of a nonspecific reactant. Hence the SGO-T activity is not related to the physiologic causes for changes in the erythrocyte sedimentation rate, white blood count or C-reactive protein.

In our hands the SGO-T activity has been a sensitive index of metastatic carcinoma. In seven of 22 patients with proved metastatic carcinoma of the liver all the tests for liver function which were done were within normal limits but the SGO-T was significantly elevated. This experience has been extended to more than 30 such instances. In addition, the test has been of use in evaluating the significance of alkaline phosphatase elevation, since the SGO-T is normal when the phosphatase is elevated as a result of bone disease or bone metastasis but rises when concomitant alkaline phosphatase elevation is due to liver disease including liver metastases.

Conclusions

1. Serum glutamic oxalacetic activity is impressively elevated following acute liver cell injury due to CCl_4 poisoning, infectious hepatitis or homologous serum hepatitis.

2. The SGO-T activity in patients with acute liver cell damage is usually many times that seen in obstructive jaundice.

3. Cirrhosis of the liver may be associated with normal SGO-T activity with mildly elevated levels and with high activity. Further study is needed to explain the significance of variation in SGO-T activity associated with cirrhosis of the liver.

4. Serum glutamic oxalacetic transaminase activity appears to be an index of liver cell injury and does not necessarily correlate with the usual tests of liver dysfunction.

5. An increase in SGO-T activity appears to be a relatively sensitive index of liver metastases.

6. The level of the SGO-T activity in liver disease has not been found to parallel or correlate with the tests of liver function commonly in use. When elevated, the SGO-T activity appears to indicate liver cell destruction and not liver cell function.

Acknowledgments

The authors are indebted to Dr. David P. Barr, Dr. Rulon Rawson and Dr. Edwin P. Maynard for permission to study clinical material at New York Hospital, Memorial Center for Cancer and Allied Diseases, and Brooklyn Hospital, respectively.

We are indebted to Dr. I. J. Van Elk, Dr. Robert J. Zullo and Dr. Gordon McGill for their close clinical coöperation and for collection of some of the data, and to Dr. David E. Molander, who collaborated with us on the experiments upon rats given carbon tetrachloride.

We also wish to express our appreciation for the technical help of Mr. Martin Podgainy and Mr. Albert Friedman.

Summario in Interlingua

Transaminase oxalacetic glutamic es extensemente distribuite in texitos animal. Illo occurre in concentrationes major in le musculo cardiac e—in ordine retrogradente —in le musculos skeletal, le cerebro, le hepate, e le renes. Omne le seros human que esseva essayate per nos monstrava un activitate de transaminase oxalacetic glutamic. In le caso de seros ab individuos normal le activitate variava ab 5 a 40 unitates.

Le activitate enzymic esseva determinate spectrophotographicamente per un simple e rapide methodo. Le nivello de transaminase oxalacetic glutamic del sero es marcatemente elevate post acute lesiones del cellulas hepatic causate per toxicosis a tetrachlorido de carbon, per hepatitis infectiose, e per hepatitis a sero homologe. Alterationes significative del transaminase oxalacetic glutamic del sero esseva observate in patientes con obstruction biliari extrahepatic, con cirrhosis, e con primari o metastatic morbo neoplastic del hepate. Le nivello del transaminase oxalacetic glutamic del sero pare esser un indice del lesion del cellulas hepatic, sed illo reflecte un parametro de morbo hepatic non identic con le parametro reflectite per le currente essayos laboratorial del functionamento hepatic. Excepte in casos de evidente lesiones del texito hepatic o del musculo cardiac o skeletal, le nivello del transaminase oxalacetic glutamic del sero non se monstrava elevate in patientes con morbose conditiones infectiose, neoplastic, degenerative, metastatic, reactive, o congenite. Usate como adjuncto laboratorial, le determination de transaminase oxalacetic glutamic del sero pare esser un promittente technica in le studio de morbo hepatic experimental e clinic.

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THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF ACUTE MYOCARDIAL ISCHEMIA * †

By Gordon B. Myers, M.D., F.A.C.P., and Frederick N. Talmers, M.D.,‡ *Detroit, Michigan*

Myocardial ischemia may be referable to (1) primary reduction in oxygen delivery by the coronary tree; (2) primary increase in cardiac work so that an oxygen supply ordinarily sufficient at rest is no longer adequate; (3) combinations of (1) and (2). Severe prolonged ischemia results in left ventricular infarction, which is manifested by distinctive QRS alterations in leads facing the epicardial surface. These consist of (1) increase in the duration and amplitude of the Q wave at the expense of the succeeding R, provided the septal vector maintains its normal left-to-right direction, or (2) development of incomplete or complete left bundle branch block in the event that the septal vector is reversed to a right-to-left direction. The QRS changes in infarction have been discussed in detail in previous publications and are beyond the scope of this communication. Myocardial ischemia, not sufficiently severe and/or prolonged to produce the foregoing QRS changes, may be manifested by diagnostic abnormalities in the ST-T complex.[1] Since no single manuscript from the vast literature would appear to cover the subject fully, an attempt will be made to present a concise descriptive analysis of "spontaneous" and induced S-T displacements in controls and in patients with coronary disease.

Spontaneous S-T Displacements

The use of the term implies that the electrocardiographic changes were not induced by the physician, but rather developed "spontaneously" or from known cause. A study of the electrocardiograms of patients who subsequently came to autopsy constitutes the basis for the differentiation of ST depression in patients without coronary disease from that associated with subendocardial ischemia.

The problems arising in the differential diagnosis of "spontaneous" ST depression are exemplified by figures 1, 2 and 3. Examinations of the patient in figure 1 revealed no physical or electrocardiographic abnormalities prior to March 2, 1953. After surgical repair of a hernia on that date, femoral artery thrombosis developed and the patient was moribund when

* Presented as a Morning Lecture at the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 8, 1954.

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† Supported in part by grants from the National Heart Institute and Michigan Heart Association.

‡ Public Health Research Fellow of the National Heart Institute.

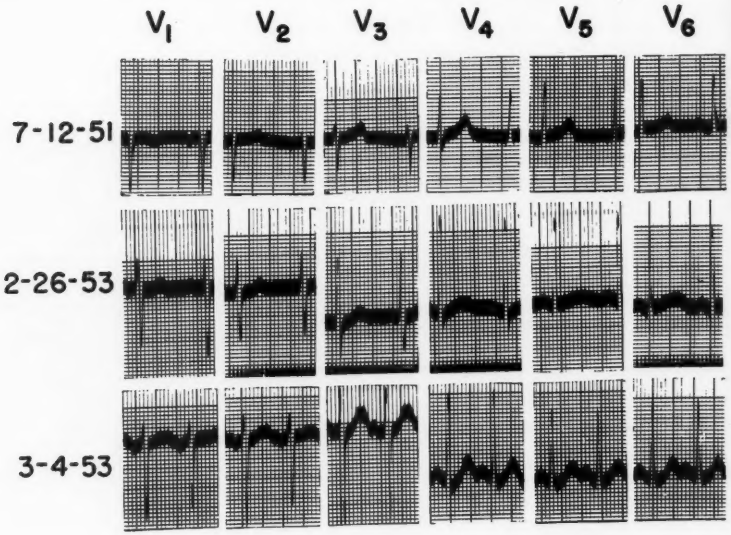

FIG. 1.

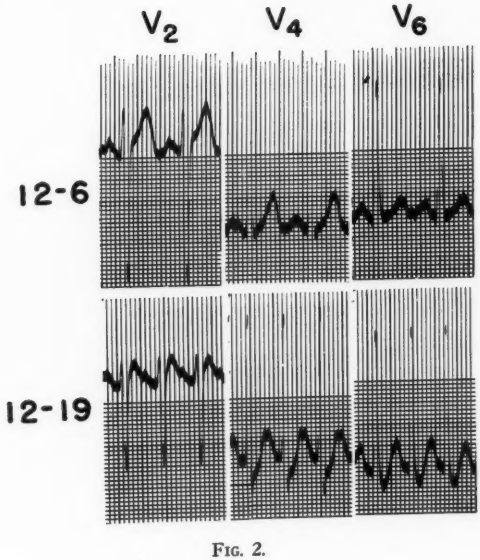

FIG. 2.

the electrocardiogram of March 4 was obtained. The first two tracings showed heart rates of 85 to 95 and iso-electric ST segments; the last tracing on March 4 showed a heart rate of 135 and apparent ST depression in V_4, V_5 and V_6. The depression of the ST junction in V_4, 2 mm. below the apparent TP segment, could be disregarded on the basis that the rapid rate may not have permitted the TP segment to reach the iso-electric level. In this same lead, the ST junction is 1.5 mm. below the PR junction,* a depression quantitatively sufficient to be regarded as pathologic;[2] however, the shape of the ST segment (continuous ascent in a curve with upward concavity) is normal and prompts a search for some other reason for the 1.5 mm. depression. The explanation is suggested by the observed increase in the amplitude of the P wave between February 26 and March 4, and the fact that this is usually accompanied by an exaggeration of the T_P waves. The development of a prominent T_P wave in leads $V_{4,5,6}$ is evidenced by its beginning descent between the P and R waves and the continuity with the

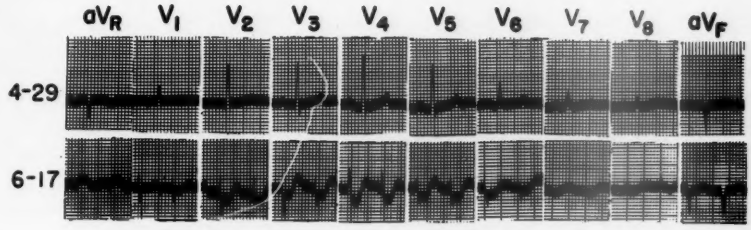

FIG. 3.

curve after registration of the QRS. This part of the tracing records the end of the T_P wave superimposed on the first part of the ST segment. Thus, the normal concave ascent of the ST segment, together with the exaggerated T_P wave, indicated that the depression of the ST junction, 1.5 mm. below the PR junction in lead V_4, was a normal variant. This was borne out by the autopsy, performed after postoperative death on March 4, which showed a normal heart, weighing 290 gm., and a normal coronary tree.

The problem is further illustrated by the extreme example in figure 2. On December 6 there was clinical evidence of moderate thyrotoxicosis, a sinus rate of 115, iso-electric ST junctions, and normal concavely ascending ST segments in V_4 and V_6. On December 19 there was a sinus rate of approximately 190 and superimposition of the exaggerated P wave on the T wave in V_4 and V_6, thereby obliterating the TP segment. Although the PR segment showed a precipitous drop, the PR junctions were 4 mm. above the ST junctions in both V_4 and V_6. The fact that the ST segments rose

* The PR junction refers to the level of the tracing at the junction of the ending of the PR segment and onset of the QRS, irrespective of whether the latter begins with a Q or an R wave.

progressively in concave ascents along with exaggerated TP waves indicated that the ST junctions, as much as 4 mm. below the PR junctions, were the result of pseudodepression in this case. The patient was in thyroid crisis on December 19, which proved fatal, and autopsy showed a negative heart and a normal coronary tree, both by histologic examination and by roentgenogram after injection with lead acetate.

The electrocardiograms reproduced in figure 3 depict the spontaneous development of ST depression that must be differentiated from that in figures 1 and 2. The patient was a man, aged 74, who had an electrocardiogram on April 29 that showed marked counterclockwise rotation but was otherwise considered within normal limits. Nearly two months later he was re-admitted in collapse from heat exhaustion, but received no cardiac glycosides. The Q waves in $V_{2,3,4}$ of June 17 showed only a slight absolute increase over those in the same leads of April 29, but had become relatively large in proportion to the succeeding R waves. The significant QRS alteration in these leads and also in $V_{5,6}$ was a decrease in the amplitudes of the R waves and an exaggeration of the S waves. This pointed to a reduction in forces associated with activation of the anterolateral aspect of the left ventricle.[3] The most striking change is in the ST segments of V_{2-6}, which show depressions of 2 to 4 mm. below the PR junctions. Although these ST depressions do not exceed those of figure 2 in magnitude, they are readily recognized as abnormal by the horizontal or downwardly sloping course of the ST segments and are representative of acute subendocardial injury.[4, 5, 6] The development of ST elevation in Lead aV_R is the typical manifestation in a lead facing the cavities.[7] The diagnosis was confirmed at autopsy, which showed marked congestion, petechial hemorrhages and patchy acute myocardial degeneration in the subendocardial portion of the anterolateral wall.

Figure 4 is concerned with spontaneous upward, instead of downward, displacements of the ST junctions. The patient was a man, aged 36, with a classic history of angina pectoris. The findings on March 11, 1949, were compatible with the left ventricular hypertrophy evident on clinical and roentgen examination. The tracing at 9:45 a.m. was obtained shortly after the onset of a severe spontaneous attack of angina pectoris; that at 10:30 a.m. was taken after recovery. The reduction of the R wave in $V_{4,5,6}$ and aV_F at 9:45 a.m., even in the absence of any increase in Q waves, suggested a mechanism analogous to that discussed in connection with figure 3, but the failure of resumption of the former amplitude after subsidence of the attack at 10:30 a.m. did not support this hypothesis. The striking changes consisted in transitory (1) elevation of the ST junctions of 4 to 6 mm. in the left ventricular leads, (2) straight sloped ascent of the ST segments, and (3) monophasic upright in place of the previously inverted T waves.[8] Similar transitory ST elevations have been encountered rarely in angina pectoris,[9] and are presented as a contrast from the more common pattern

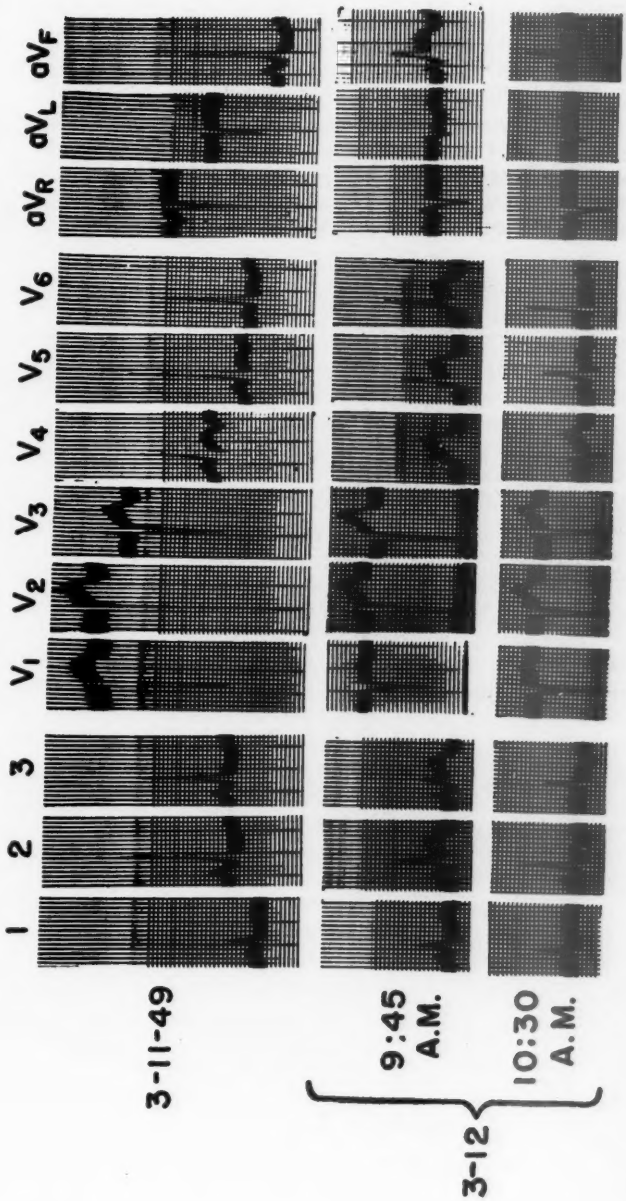

FIG. 4.

of transitory ST depression. ST elevation of this type is indicative of transitory injury of the subepicardial layer of myocardium [10] and may occur when the injury is confined to this zone, or when it extends through the thickness of the cardiac wall. Abnormal monophasic ST elevation is encountered early in myocardial infarction, followed by the characteristic QRS abnormalities and by progressive inversion of the T waves.

When spontaneous angina pectoris is accompanied by abnormal ST displacement, ischemia, induced in the same patient by exercise or anoxia, will be manifested by similar electrocardiographic changes.[11, 12, 13] Thus, the ST patterns in the absence or presence of significant coronary disease at autopsy, form the basis for the interpretation of induced ST displacements.

Methods for the Induction of Electrocardiographic Changes

The methods used to attempt to induce electrocardiographic manifestations of myocardial ischemia fall into three general groups: (1) deliberate reduction in oxygen delivered by the coronary tree, (2) intentional increase in cardiac work, (3) combinations of (1) and (2).

The best known test based upon the deliberate reduction in oxygen delivered by the coronary tree has been standardized by Levy and associates,[14, 15] and has been used extensively.[16, 17] Others have advocated tests in which coronary constriction was apparently induced reflexly by application of cold,[18, 19] or pharmacologically by coronary constrictors, such as Pitressin [20] or ergotamine,[21, 22, 23] which carry the potential danger of critically reducing a previously impaired coronary circulation. In this clinic, the Levy test has had a thorough trial; coronary constrictors have not been employed intentionally.

The best known test based upon deliberate increase in cardiac work has been standardized by Master and associates [24] and has been widely adopted. Some have attempted to augment the work of the Master two-step test by continuation of the exercise until fatigue or pain,[25, 26] by performance of the test after a heavy meal,[26] or by supplementary application of ice.[26] Others have substituted for the exercise the load of a heavy meal [27, 28] or an intravenous injection of hypertonic glucose.[29]

In this clinic, extensive use has been made of a modified Master test. The test is used for diagnostic purposes only on those patients in whom there is a suspicion of coronary insufficiency but no clearcut history of angina pectoris, no evidence of myocardial infarction, or no other contraindication to the exercise. If the single two-step test is negative, the double test is performed; if the double test is negative but the suspicion of coronary insufficiency still prevails, an attempt is made to duplicate the effort that induced the pain in question. The test is used for prognostic purposes in ambulatory patients after recovery from myocardial infarction. The object is to evaluate the competence of the collateral coronary circulation for two-step climbing, individualized to match the activity in which the patient is

currently engaged, or the increase in allowance that is contemplated. The criteria for the interpretation of the electrocardiogram differ from those of Master and will be given below.

Detailed comparisons of the Levy and Master tests have sometimes favored the former [30] but more often the latter.[31, 32, 33] In this clinic the exercise test has yielded a higher incidence of positive electrocardiographic findings in known coronary disease, yet a lower incidence of untoward symptoms. By careful patient selection and supervision, serious complications are very rare, but cannot be completely eliminated, as long as tests are performed on patients with coronary disease. Furthermore, two-step climbing more closely approximates physiologic demands than the Levy test, and the response provides a better estimate of tolerance of daily activities. The Levy test is now reserved for those unable to climb steps for some extracardiac reason, and for those in whom drug evaluation is necessary at physical rest.

The criteria for the distinction between normal and abnormal responses to exercise or anoxemia [2, 34, 35, 36] include (1) ST displacement, (2) QRS contour, (3) T wave voltage and direction, (4) changes in rhythm, and will be considered in reverse order. Newly appearing ectopic beats or rhythm after exercise [37] are suggestive of myocardial ischemia, but this diagnosis is not made in this clinic unless significant ST displacement, QRS alterations or clinical manifestations are also present. A normal upright T wave in the control tracing is prone to an isolated decrease in amplitude during exercise or anoxemia, as illustrated by the electrocardiograms of a healthy medical student, reproduced in figure 5.* The tracings in figure 6

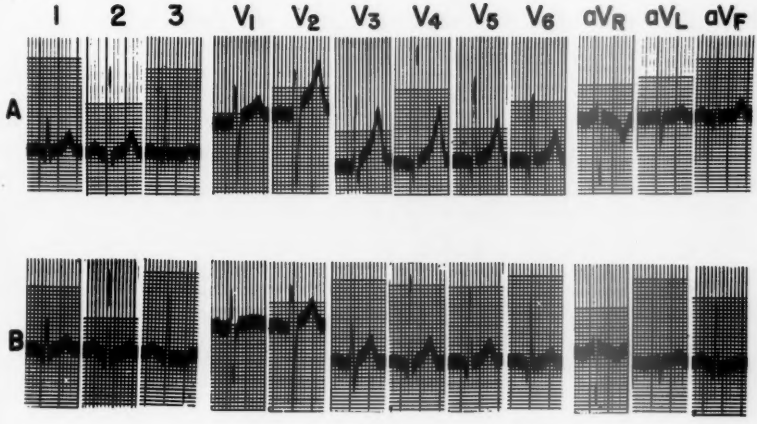

FIG. 5.

* Figures 5, 6, 10, 12, 13 and 14 were obtained by Dr. Marshall MacDonald in an unpublished study of the Levy test.

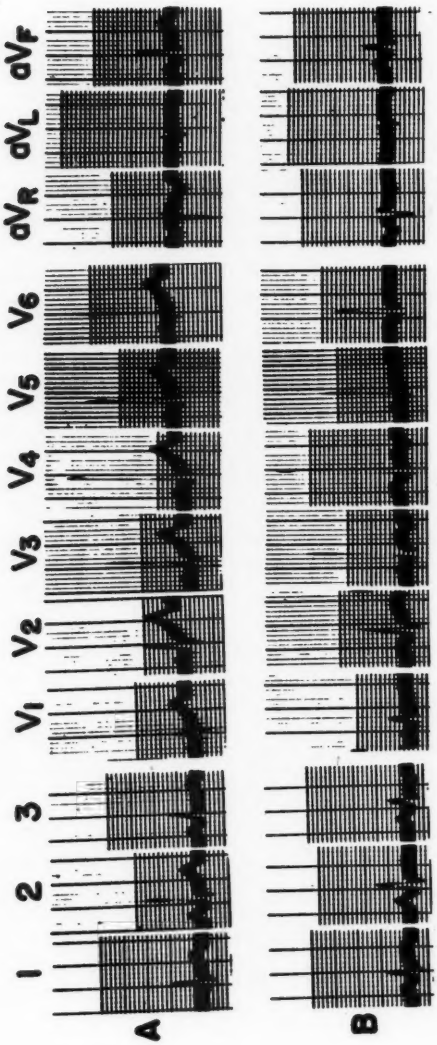

FIG. 6.

were obtained on a normal young resident who had a completely negative cardiovascular history, physical and roentgen examination and has remained well for the six years that have elapsed since this study. The control tracing was negative, but thereafter the Levy test showed T wave inversion without ST displacement. Changes comparable to those of figure 6 have been observed in others without clinical evidence of organic heart disease, and are differentiated from those of myocardial ischemia by (1) the absence of abnormal ST displacement in contrast to the characteristic horizontal or sagging ST depression in angina pectoris, (2) the shortening of the QT interval in cases comparable to that in figure 6 in contrast to the maintenance or prolongation in angina, (3) the prevention of T wave inversion by ergotamine preliminary to exercise in patients without organic heart disease,[23] but not in abnormals. Alterations in intraventricular conduction, such as transitory left bundle branch block, precipitated by the exercise or anoxemia test, are rare and may reflect a latent defect uncovered by acceleration in cardiac rate or ischemia.

Significance of Contour As Well As Degree of Induced ST Displacements

The interpretation of the exercise or anoxemia tests depends primarily on the comparison of the ST segments in the tracings taken beforehand and afterward. The return of a normally elevated ST junction to the isoelectric line during exercise or anoxemia is well known,[38] and is illustrated by figure 5. The level of the tracing just before the registration of the P wave has been used as a reference point from which the ST junction has been measured,[34] and errors have been traced to lack of an iso-electric ST segment due to tachycardia.[26, 39] Although this source of error has been circumvented through the use of the PR junction as the reference point,[2] due consideration often has not been given to the influence of the T_P wave or the shape of the ST segment.

Figure 7 shows the effects of exercise more strenuous than the double Master test on the electrocardiogram of a medical student who was believed to have a normal heart on history, physical and roentgen examination. The control electrocardiogram at rest was considered normal. After exercise, the ST junction became depressed from 0.5 to 0.75 mm. below the PR junction in Leads II, $V_{4, 5, 6}$ and became depressed 1 mm. or more below the T segment in Leads II, $V_{5, 6}$. This degree of depression might be classed as abnormal, if cognizance were not taken of the shape of the ST segment. In all leads after exercise the ST segment remained normal in shape, i.e., it showed a progressive ascent to the T wave with preservation of upward concavity. The PR segment showed an exaggerated downslope in all cycles of Leads II, $V_{4, 5, 6}$, not merely in the isolated complexes reproduced in figure 7. The effects of an exaggerated T_P wave continuing after the termination of the QRS were largely responsible for the apparent depression of the ST

junctions. Although the electrocardiographic response to exercise is considered normal in this healthy medical student, it has been shown that vigorous exercise (walking on a treadmill at 10% grade) in combination with anoxia evoked by the simultaneous breathing of 11.3% oxygen will produce ST depression that is abnormal in configuration, as well as in degree, in persons who are clinically normal.[40] The experience with this and other comparable electrocardiograms in apparently normal subjects indicates that a positive test should be based upon an abnormal ST configuration, as well as an abnormal degree of junctional depression, as emphasized by Wood et al.[41] The electrocardiographic findings were not altered by cardiac glycosides in any of the illustrations, since such drugs were not given prior to the studies. Furthermore, there was no evidence of hypokalemia.

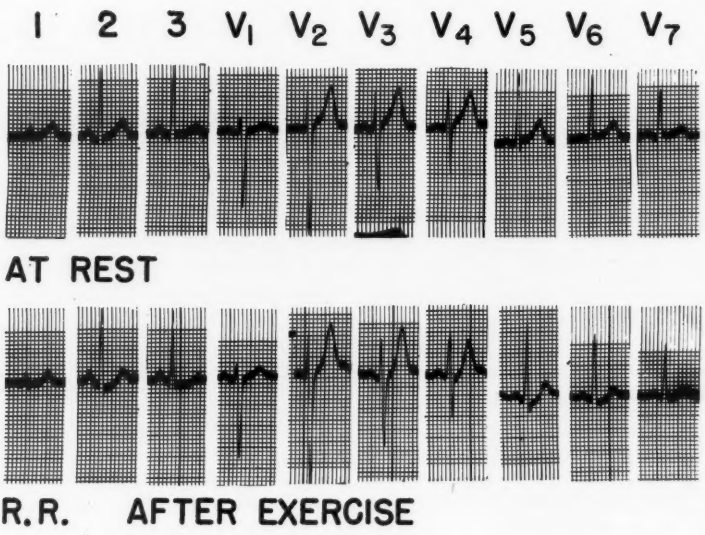

FIG. 7.

Figure 8 reproduces Lead V_4 of three patients with angina pectoris before and after exercise. The ST junction is depressed 1 mm. after exercise in cases 1 and 3; this depression is recognized as abnormal from the fact that the entire segments are displaced horizontally downward. An alternative abnormality in contour is a downward sagging of the depressed ST segments, exemplified by Leads V_{4-6} of tracing B of figure 13. On the other hand, case 2, figure 8, shows a 2.5 mm. junctional depression after exercise, followed by a progressive concave ascent of the segment. Since there was no evidence of tachycardia or exaggeration of the T_P wave, this was considered a true and not a pseudodepression of the S-T junction, and was deep

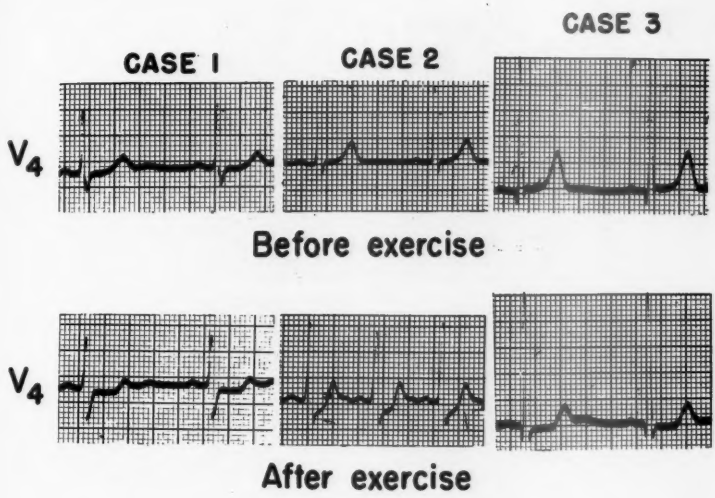

FIG. 8.

enough to constitute evidence of subendocardial ischemia. When a given lead shows ST depression of sufficient depth to be classified as abnormal, but not of the characteristic shape, neighboring leads may show typical horizontal or downwardly sagging ST segments. This was exemplified by Lead V_6 of case 2, which was not reproduced in figure 8.

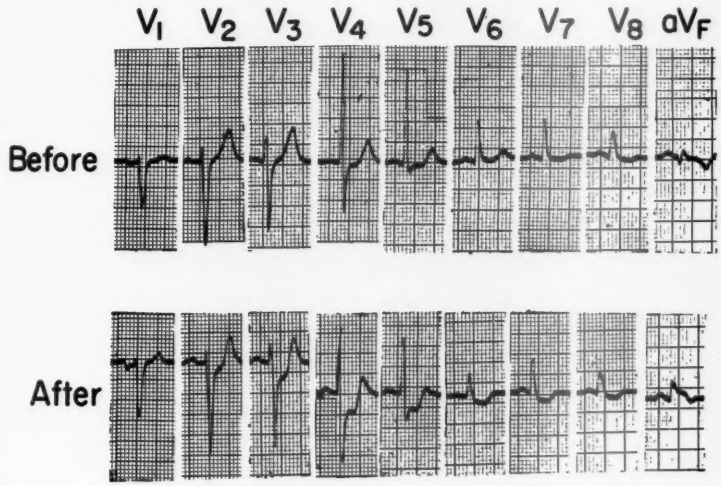

FIG. 9.

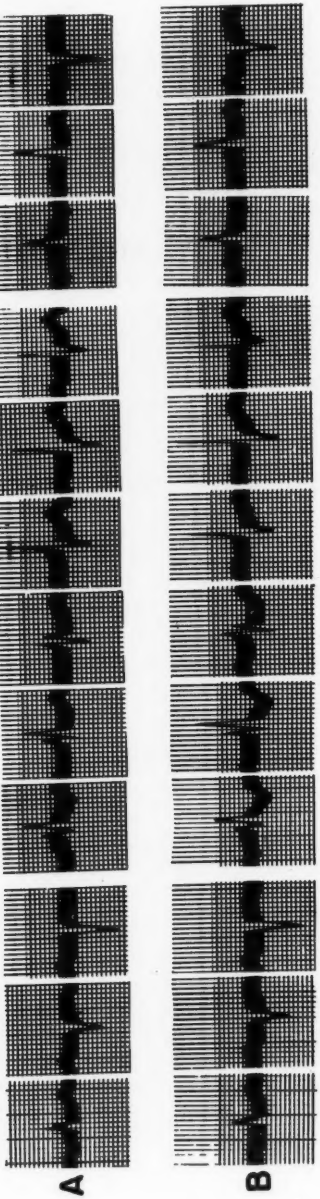

FIG. 10.

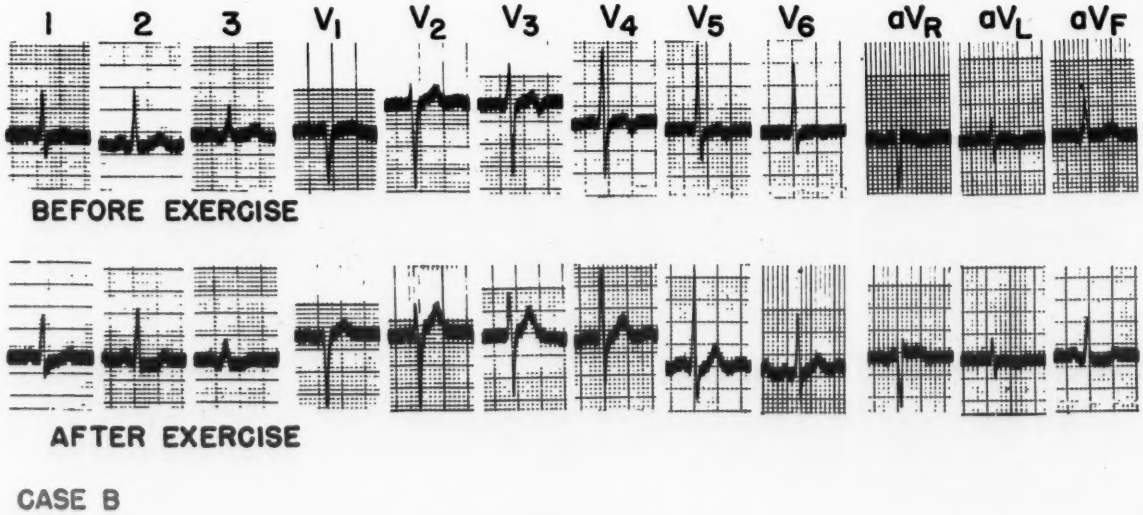
1
2
3
V1
V2
V3
V4
V5
V6
aVR
aVL
aVF
BEFORE EXERCISE
AFTER EXERCISE
CASE B

FIG. 11.

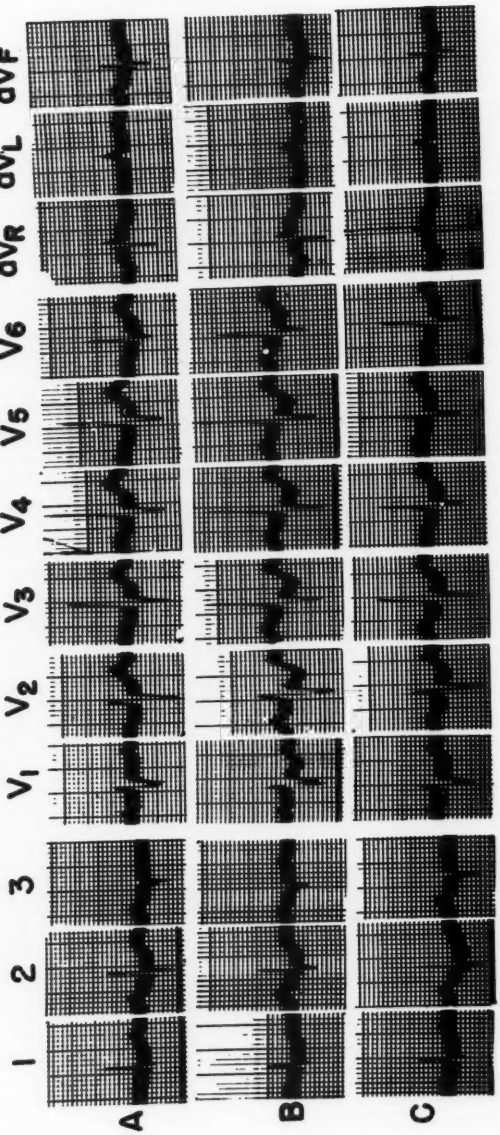

FIG. 12.

Scrutiny of the resting electrocardiogram is indicated to detect changes in the ST segment which might have formed the basis for the prediction of abnormal exercise tests. The horizontal course or slight downslope of the ST segment for .12 sec. or more prior to the inscription of the T wave in the control tracings of Lead V_4 of case 1, figure 8; Leads $V_{7,8}$ of figure 9; Lead V_2 of figure 10; Leads $V_{3,4,5}$ of figure 12 A; Leads $V_{5,6}$ of figure 14 A, is sufficient to arouse suspicion that exercise might yield positive findings. The performance of the Master test establishes the diagnosis in such cases. On the other hand, control Leads V_4 of cases 2 and 3, figure 8, were not suspicious, and the exercise tests that established the diagnosis were carried out on the basis of history. Thus, the position and contour of ST segment in the resting electrocardiogram often, but not always, serves as a clue of myocardial ischemia that can be precipitated by exercise.

The resting electrocardiogram of figure 9 shows (1) the QRST contour of organized posterior diaphragmatic infarction in Lead aV_F, (2) the U-shaped ST depression in $V_{7,8}$ presumptive of exercise-inducible ischemia, and (3) ST depression of $V_{4,5}$ of abnormal magnitude, but not shape. The fact that exercise produced an abnormal increase in U-shaped ST depression

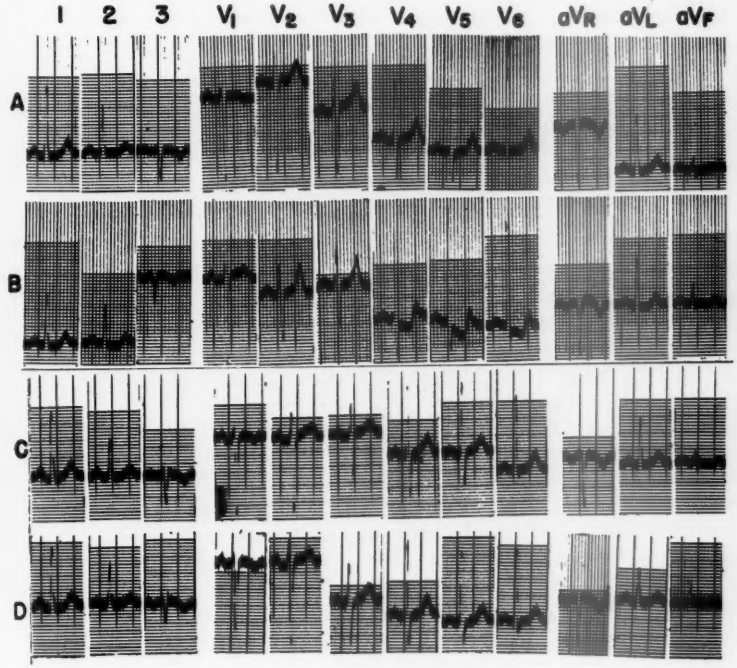

FIG. 13.

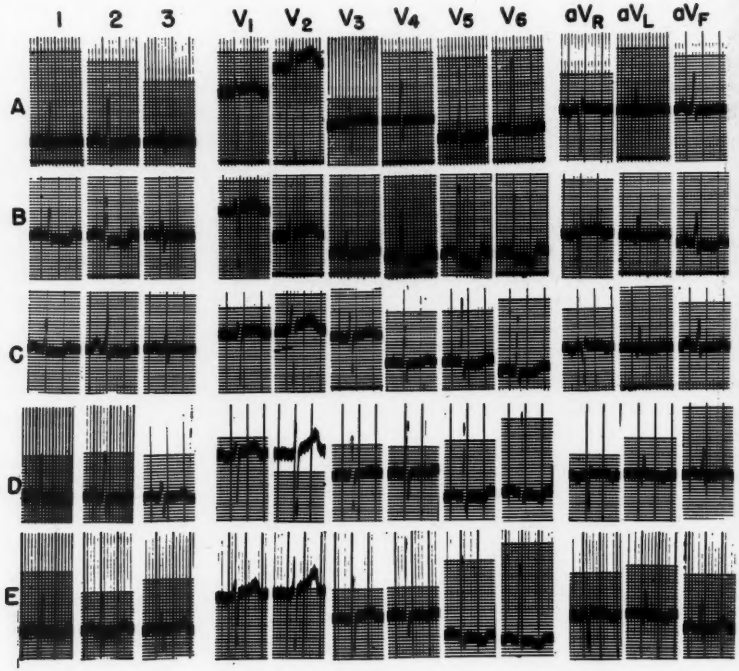

FIG. 14.

in $V_{6,7,8}$ confirmed the suspicion of ischemia of the posterolateral wall; the observation that exercise produced an even greater depression in $V_{4,5}$ with a horizontal or sagging contour indicated that these leads were likewise positive. Before arrival at a final conclusion as to the mechanism of the abnormal ST depression in V_{3-8}, inclusive, the significance of acute ST elevations elsewhere must be evaluated. If the portion of the ventricular wall opposite to Leads $V_{3,4,5,6,7}$ and/or $_8$ were inert, it would have produced no forces during cardiac repolarization, but would merely have transmitted those arising elsewhere. The abnormalities registered as ST depression in the anterolateral precordial leads would have been recorded as upward displacement in cavity leads,[42] but were not believed responsible for the ST elevation in aV_F, because the well developed R wave in this lead suggested that living subepicardial muscle in the posterior diaphragmatic wall, rather than the cavity, would have dominated the record in Lead aV_F. If this interpretation is correct, the exercise-induced ST elevation in aV_F indicated ischemic injury of the subepicardial layer of the partially infarcted diaphragmatic wall. Subepicardial ischemic injury is manifested not only by ST elevation in overlying leads (aV_F in this case), but also by ST depression

in cavity leads, and perhaps in leads facing the opposite ventricular wall. However, an exercise-induced lesion of the diaphragmatic wall could not have been the major cause of the ST depression in $V_{3,4,5}$ for two reasons: (1) the relatively small magnitude of the elevation in aV_F as compared to the depth of the depression anteriorly, and (2) the comparatively small area of subepicardial injury, as indicated by the limitation to Lead aV_F facing the diaphragm, and the registration of depression rather than elevation in Lead V_8 facing the back.

Significance of the Leads in Which Induced ST Displacements Are Registered

"Spontaneous" or induced ischemic injury is prone to a ringlike distribution around the inner circumference of the left ventricle, as evidenced by the registration of comparable ST depressions in leads facing the opposite anterior and posterior surfaces of the left ventricle (e.g., V_4 and V_8), and the postmortem demonstration of infarction [6] or patchy myomalacia [43] distributed throughout the inner circumference of the subendocardial portion of the left ventricular myocardium. Abnormal ST depression induced in Leads V_3, V_4, V_5, V_6, V_7, V_8 under such circumstances is illustrated by figure 9.

A negative Levy test in persons with known coronary disease has been attributed to mutual cancellation of effects from opposite walls.[44] Whereas the failure of development of abnormal Q waves in some of our patients with postmortem ringlike subendocardial infarction was believed attributable to a relatively uniform thickness of the lesion,[6] failure of development of abnormal ST depression has not been observed in our material for the same reason. Negative Levy or Master tests in patients with known coronary disease may be attributable to the development of a good collateral circulation,[45] to insufficient stress,[44] or to failure to obtain the proper leads.[44]

In Levy and Master tests, abnormal ST depression is always greater in some leads than in others, and is often limited to a few leads. Positive findings are much more common in Leads V_4 and V_5 facing the anterior and/or anterolateral aspect of the left apex (figure 13 B), reflecting ischemic injury of the subendocardial layer in this area, presumably from insufficiency of the anterior descending coronary artery.

Ischemic injury of the septum, as well as the anterolateral wall of the left ventricle, is exemplified by figure 12 B, in which anoxemia produced typical ST depression in Leads V_1, V_2, as well as in Leads V_{3-6}. Ischemic injury more localized to the septum is exemplified by figure 10, from a patient with angina pectoris and right bundle branch block in the resting tracing. During the Levy test, significant ST depressions occurred in Leads V_{2-3} facing the right side of the septum and right ventricle, but not in Leads V_{4-6} facing the left ventricle.

Figure 11 reproduces findings that are relatively uncommon in angina pectoris.[46] The QRS complexes were considered normal throughout, both

in the resting and post-exercise tracings. Leads V_{3-6} displayed convex ST segments and terminally inverted T waves in the control tracing, but isoelectric concave ST segments and upright T waves after exercise. This was a change from abnormal ST-T complexes, not to normal, but rather to reciprocally upright T waves, as suggested by a study of the unipolar leads. In Lead aV_R, exercise produced a 1 mm. ST elevation significant of acute subendocardial injury. The injured zone is located posteriorly, as shown by the U-shaped ST depression in Lead aV_F after exercise. A greater downward displacement would have been expected in esophageal leads or $V_{7,8}$ or $HV_{7,8}$, but these leads were not obtained.

In figure 11 the standard limb leads were positive after exercise, but were not nearly so helpful as the remaining leads, which permitted localization of the ischemic injury to the subendocardial portion of the posterior wall. In many cases, electrocardiographic evidence of acute subendocardial injury is demonstrable after exercise or anoxemia in thoracic leads, but not in standard limb leads (e.g., figure 10, figure 13 B). On the other hand, no case has been observed in which the test was regarded as negative from semidirect leads but positive from standard limb leads, if caution was employed to exclude pseudodepression in Lead II from an exaggerated T_P wave. On the basis of experience in this clinic, it is recommended that the leads be taken in reverse order after exercise or anoxemia, namely, V_8, then V_7, V_6, V_5, V_4, V_3, V_2, V_1, aV_F, aV_L and aV_R. If there are abnormalities in aV_L, or if there are any other reasons to suspect injury of the subendocardial aspect of the base, Leads HV_8, HV_7, HV_6, HV_5, HV_4 and HV_3 should be taken. It is important that the same posture be employed, and that the electrode be applied at exactly the same points, accurately marked when the first tracing is taken.

Serial Electrocardiographic Evaluation of Therapy

The effect of a drug or other therapeutic procedure in patients with known coronary disease can be evaluated by the Levy or Master test, utilizing not only subjective but also, in particular, objective criteria.[47, 48] Figures 12, 13 and 14 exemplify evaluation by electrocardiograms obtained before and after the Levy test.

Figure 12 was obtained on a woman with angina pectoris six years after she had been hospitalized with serial electrocardiographic changes typical of posterior infarction. Although concurrent esophageal leads were diagnostic of old healed posterior infarction, the only residue in the 12 lead electrocardiogram (figure 12 A) was a QRS pattern in aV_F, attributed to the posteroseptal portion of the infarct. However, the resting tracing did display slightly depressed horizontal or sagging ST segments in the precordial leads that should have prompted a Levy or Master test in the absence of a positive history. The markedly depressed, sagging ST segments in Leads V_{1-6} during anoxia (figure 12 B) indicated ischemic injury of the

subendocardial portion of the septum and anterolateral wall. The administration of 0.6 mg. nitroglycerin while the inhalation of 10% O_2 was continued (figure 12 C) showed partial electrocardiographic restitution, and exemplified the well known pharmacologic action of the drug.

Figures 13 A and B were obtained before and after a Levy test in a woman with hyperthyroidism and angina pectoris; figures 13 C and D represented a repetition several months later, after a successful subtotal thyroidectomy, when she was completely symptom-free. The first pair of tracings showed that anoxemia precipitated typical evidence of subendocardial injury in Leads $V_{4, 5, 6}$; the last pair of tracings showed that a similar test failed to provoke any significant electrocardiographic changes.

Figure 14 was obtained on a patient with syphilitic aortic insufficiency and angina pectoris. The control tracing (figure 14 A) showed horizontal or sagging ST segments in the left precordial leads, which should have prompted a provocative test in the absence of a history. ST depression significant of subendocardial injury occurred during anoxemia (figure 14 B), and was nearly reversed by the administration of nitroglycerin during continuation of the Levy test (figure 14 C). A course of potassium iodide had no effect upon symptoms or Levy test (not reproduced); however, a standard course of penicillin gave improvement not only in clinical symptoms but also in tolerance of anoxemia. The control electrocardiogram showed slight upward convexity of the ST segment in V_6 (figure 14 D). A more rounded ST curvature and inverted T wave are commonly found in resting tracings of patients with left ventricular hypertrophy, in the absence of appreciable coronary disease. The absence of any significant change during anoxemia (figure 14 E) was in keeping with improved tolerance, both clinically and by the Levy test.

Summary

By correlation of "spontaneous" ST changes in serial electrocardiograms with autopsy findings, the pseudodepression associated with tachycardia and exaggeration of the T_P wave is distinguished from abnormal depression secondary to acute subendocardial injury. In the former the ST segment displays a continuous ascent in a curve with upward concavity; in the latter it exhibits a characteristic horizontal or sagging depression of 1 mm. or more in the absence of cardiac glycosides.

Both the Levy and Master tests have been used extensively for the induction of electrocardiographic changes; the latter method is preferred in this clinic. It is employed for diagnostic purposes when there is a suspicion but no clearcut evidence of coronary insufficiency; it is utilized for prognostic purposes in asymptomatic ambulatory patients after recovery from myocardial infarction to evaluate tolerance of prescribed activity. Changes in the ST segment of the resting electrocardiogram that might have formed the basis for the prediction of abnormal tests are emphasized. Induced

pseudodepression, manifested by an ST junction, dropping 0.5 mm. or more below the PR junction, and an ST segment, continuously ascending in a concave arc, is distinguished from the abnormal findings characterized by an ST junction, depressed to an equal or greater degree, and a horizontal or sagging depression of the ST segment. Abnormal ST displacements are much more frequent in Leads $V_{4,5}$, facing the anterior or anterolateral aspect of the apex. Electrocardiographic evidence localized to right precordial leads may be associated with septal ischemia; evidence localized to back leads and/or aV_F may be associated with posterior ischemia. The standard limb leads are not positive nearly so frequently as the chest leads and have shown no abnormalities that are not better evaluated by multiple chest leads. The effect of various therapeutic procedures in patients with abnormal Levy tests is exemplified.

SUMMARIO IN INTERLINGUA

Le correlation de "spontanee" cambiamentos de ST in electrocardiogrammas serial con constatationes autoptic permitte le distinction del pseudodepression associate con tachycardia e exaggeration del unda TP ab le depression anormal que seque acute lesiones subendocardial. In le prime de iste casos, le segmento ST exhibi un continue ascendita secundo un curva con concavitate verso le alto; in le secunde caso, le segmento ST exhibi un depression characteristicamente horizontal de 1 mm o plus con absentia de glucosidos cardiac.

Le probas de Master e de Levy ha essite empleate extensemente pro inducer cambiamentos electrocardiographic. Le methodo de Master es preferite in le practica del autores. Illo es empleate pro objectivos diagnostic in casos de suspicion sin evidentia definitive de insufficientia coronari. Illo se emplea etiam pro objectivos prognostic in le casos de ambulante patientes sin symptomas post lor recuperation ab infarcimento myocardiac. In tal casos illo permitte un evalutation del toleration del prescribite grado de activitate. Es sublineate le facto que certe cambiamentos del segmento ST in electrocardiogrammas obtenite in stato de reposo es de importantia special in tanto que lor correcte interpretation poterea formar le base del prediction de tests con resultatos anormal. Es signalate le sequente distinction: Pseudodepressiones se manifesta per un junction de ST que descende infra le junction PR per 0,5 mm o plus e un segmento ST que ascende continuemente in un arco concave. Depressiones anormal es characterisate per un junction ST que descende del mesme maniera o ancora plus pronunciatemente e un segmento ST a incurvation horizontal. Displaciamentos anormal de ST es multo plus frequente in derivationes V_4 e V_5 vis-à-vis le aspectos anterior o anterolateral del apice. Signos electrocardiographic que es localisate in derivationes dexteroprecordial pote esser associate con ischemia septal; signos localisate in derivationes dorsal e/o aV_F es associabile con ischemia posterior. Le derivationes standard del extremitates rende resultatos positive multo minus frequentemente que le derivationes thoracic; illos ha exhibite nulle anormalitates que non esseva melio evalutabile per multiple derivationes thoracic. Es discutite e exemplificate le effectos del varie procedimentos therapeutic que pote esser usate in patientes qui ha reactiones anormal in le proba de Levy.

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CLINICAL STUDIES OF SECONDARY AMYLOIDOSIS IN TUBERCULOSIS *

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IN 1949 the first of these cases of secondary amyloidosis in tuberculosis came under my observation. The date is important, since this general survey of amyloidosis was begun at a time when the new combined chemotherapeutic and surgical attack upon tuberculosis was to improve the prognosis even in far advanced cases.

Because reversal of amyloidosis secondary to tuberculosis has been recorded as a rare event in scattered clinical reports,[1, 2, 3] and doubt has been expressed [2] that amyloid deposits are ever re-absorbed, the subject seemed worthy of investigation. Likewise, a review of the nature of hepatic impairment in this disease was particularly suggested by Moschcowitz' [4] statement that there is "never gross evidence of hepatic insufficiency," yet hepatomegaly is a cardinal symptom. Moreover, clinical evidence of hepatic failure was wanting and the published literature on the subject almost nonexistent. Similarly, the renal lesion was considered worthy of attention despite extensive studies. Moreover, a general impression prevailed that renal failure resulting from secondary amyloidosis was a rarity.

It is an interesting and important fact that, at least up to recently, the appearance of secondary amyloidosis was regarded as a serious prognostic sign. Coming usually in the course of far advanced tuberculosis, it seemed to set a seal of doom upon the patient. It was believed to increase the surgical risk,[2] so that many candidates for surgical therapy were rejected. The extent to which amyloidosis handicaps the recovery of the tuberculosis patient or hastens his death by contributing to "general debility" or directly causes death by impairing the function of one or more of the organs appeared unclear and worthy of careful investigation.

Finally, in spite of excellent tests for determining the existence of the disease, its diagnosis still presents problems. To establish or exclude the diagnosis of secondary amyloidosis is clearly of value, particularly where enlargement of liver or spleen or albuminuria is present. Some facts gleaned from these studies will, I hope, add to the knowledge of the syndrome and contribute to diagnostic facility.

GENERAL CONSIDERATIONS

Thirty consecutive cases of secondary amyloidosis occurring during the course of tuberculous disease in patients in the Chicago Municipal Tubercu-

* Received for publication March 7, 1955.
From the Department of Medicine of Northwestern University and the City of Chicago Municipal Tuberculosis Sanitarium.

losis Sanitarium were studied. There were 21 males and nine females; 25 were Caucasians and five were Negroes. The preponderance of white males is out of all proportion to their number in the hospital population, which is regularly about 54% whites and 50% males. Pearlman [5] found no significant age, sex or race differences, but Cohen [6] found Caucasians far in the majority while the sex incidence was equal. All cases in the present series were classified as far advanced tuberculosis.

The age of the patients at the time amyloidosis was first recognized ranged from 18 to 61 years, with an average age of 36.6; 14 of the 30 patients were in the fourth decade. Cohen's [6] patients ranged from 14 to 67 years, and 66% were in the 20 to 39 year group. Dixon [7] noted the highest incidence in the third decade in postmortem material, while Rosenblatt [8] noted it in the fourth decade.

Taran's [9] modification of the Congo red test of Bennhold was relied upon as a crucial diagnostic procedure in practically all cases. It was not one of the objectives of this study to reëxamine the validity of the test, but merely to compare the results with those of other observers. Lipstein [10] in autopsy material found 34 instances of amyloid disease in 125 cases of fatal tuberculosis. All but five cases absorbed dye 90 to 100%, while these five gave values of 85, 60, 35, 35 and 35% retention. The latter figures represent false-negative tests, since all agree that values less than 90% represent false-positives. An incidence of 24.3% false-negatives is reported in one series; [11] others [12, 13] agree that insufficient deposition of amyloid to take up 90% or more of the dye accounts for the high incidence of false-negatives. In the present group, 21 patients showed 100% dye retention, and all but two patients, 90% or higher. Of the latter, one had 35% retention but was considered on other grounds to have amyloidosis. He died four months later and showed very extensive involvement. The other had 60% retention initially but nine months later this had risen to 100%. Two others showed an increase of dye retention from 15% to 100% in seven months, and from 30% to 95% in six months, respectively. Of the seven patients of the original group still alive, three had 90% and four 100% retention of Congo red when first tested.

While it is often impossible to assign more than a presumptive date of onset for a case of tuberculosis as well as for the onset of amyloidosis, clinical experience permits a fairly good approximation in the majority of cases. The average interval was 4.6 years, but two cases, both female, had intervals of 12 and 13 years, respectively, so that the true mean is lower. Of the 12 cases having an interval of five or more years, five patients were females, although this sex represented only nine of the 30 cases in the group. Cohen [6] considered abnormal findings in the urine as the earliest sign of amyloidosis, and in 58 cases his estimated interval between onset of tuberculosis and the findings in the urine of amyloidosis was substantially as reported here. Moschcowitz,[4] quoting Waldenström, states

that one to two years' duration of primary disease is required before amyloid is deposited, while Holten [14] noted an interval of from six months to five years. Rosenblatt's [8] patients were ill of their primary disease for less than two years.

Hepatic Studies

A. Results of Tests: Initially a fairly large battery of tests was employed, but when it was found that some offered small hope of yielding results not obtainable by other means the redundant tests were discontinued. Of these, the galactose tolerance was performed 10 times and found normal, the prothrombin time determinations six times and found normal. Twenty-nine patients were surveyed for hepatic disease on at least one occasion, and in many instances the tests were done repeatedly over several years. The omission of studies of bile excretion from this series was deliberate, in view of the finding of normal icteric index in 12 patients tested by Tiber, Pearlman and Cohen [15] and the absence of jaundice in our patients. Indeed, there are recorded only two bona fide instances of jaundice associated with secondary amyloidosis.[16 and 17, case 3] Three other reports were all in cases of primary amyloidosis.[17, case 2, 18, 19] Another instance has been reported [20] associated with secondary amyloidosis, but it was complicated by fatal postoperative shock. In those cases where functional tests were performed, some were found normal, and no consistent pattern to the abnormal tests was observed.

Total Plasma Cholesterol was determined in 23 cases and the level found to be within normal ranges (150 to 250 mg. per 100 c.c.) in 14 instances, elevated in six and subnormal in three.

Plasma Cholesterol Esters: Of 20 cases examined, this moiety was found to equal 60% or more of the total cholesterol in only seven instances. In four of these the level was much increased above normal as part of hypercholesterolemia.

Total Plasma Proteins were measured in 28 cases and found normal (6 to 8.2 gm. per 100 c.c.) in 21, above 8.2 gm. per 100 c.c. in three, and below 6 gm. per 100 c.c. consistently in four. In five of the normals a late decline below 6 gm. % was observed.

Albumin-Globulin Ratio: This too was determined in 28 cases and found below 1.5 : 1 in 21 and within normal limits in seven.

Cephalin-Cholesterol Flocculation Test was performed in 12 cases, usually only once. In seven it was reported as "2 plus" and in four others as "3 plus."

Thymol Turbidity Test: Eleven cases were tested and elevation above 4 units was found in four. One patient with an initial test of 6 units subsequently showed only 3 units.

Bromsulphalein Excretion: Eight of 23 cases tested showed retention in excess of 10% of the dye after 1 hour. The same individual whose thymol

turbidity test changed to normal exhibited a simultaneous failure of Bromsulphalein excretion.

B. Discussion: Regarding total plasma cholesterol, Eichelberger and McCluskey [21] noted no constant trends of levels in tuberculosis (without regard to amyloidosis), but concluded that hypercholesterolemia indicated good resistance and immune response and hypocholesterolemia the opposite. King and Bruger [22] also related low cholesterol levels to poor prognosis in tuberculosis, and found hypercholesterolemia with renal amyloidosis (cf. discussion of cholesterol under "Renal Studies," below). Two of the six patients in my series who showed high cholesterol are still living, and two others whose cholesterol levels rose to normal or above are also among the seven survivors. What rôle the liver plays in this complex situation in influencing total plasma cholesterol is difficult to assess.

Cholesterol ester studies have not been reported hitherto in amyloidosis and constituted a fruitful line of investigation. It is widely recognized that esterification of cholesterol is a function of the liver [23] and constitutes a valid test. Spellberg [24] states: "The esterification of cholesterol is disturbed early in liver disease and a depression of serum cholesterol esters is a sensitive indication of hepatic disease." Values below 60% of the total plasma cholesterol are considered abnormal. The high incidence of abnormality in this series is taken as evidence of hepatic disease and a diagnostic sign of importance.

In uncomplicated tuberculosis Eichelberger and McCluskey [21] found total protein levels normal or higher with globulin averages elevated. Tiber, Pearlman and Cohen's [15] statistics do not confirm this. It is interesting that their figures for seven patients *with* amyloidosis but *without* albuminuria are substantially the same as for 31 patients with albuminuria. They found total protein depressed below 6 gm. % in a greater number of cases than did the author, but otherwise the relationship, particularly the trend to relative hyperglobulinemia, corresponds well. Cohen [6] found total protein depressed in 53% of cases, hyperglobulinemia in 24% and inversion of A:G in 63%, while Auerbach and Stemmerman report reversal of A:G in only 38% and normal total plasma protein in the majority of cases. In the author's series a concurrent lowering of A:G ratio as total protein declined was frequently noted.

Taran and Lipstein [25] found no relationship between the presence of amyloidosis per se and a positive Takata-Ara test, but concluded that the reaction depended upon alterations in albumin-globulin ratio. This was in substantial agreement with Israel and Rheinhold,[26] whom they quote, but Tiber et al.[15] found an inconsistent relationship to A:G ratio. In the present series abnormal cephalin flocculation or thymol turbidity associated with an A:G ratio below 1.5 was found in all cases except one; usually the ratio was below 1.0. Of the total of 12 cases studied, four instances of associated hyperglobulinemia were noted.

The cephalin-cholesterol flocculation test was almost universally positive. The thymol turbidity test in the four cases in which it was found elevated was accompanied by abnormal Bromsulphalein retention in three. Tiber et al.[15] found Bromsulphalein retention of over 5% per hour in two of 12 cases. The author found eight instances in 23 cases tested.

Hepatomegaly was almost uniformly noted in the present series at some time in the course of the illness. Palpable liver was recorded in 20 cases, while in an unspecified number of patients reëxamination revealed enlargement where previously it had been absent. Only albuminuria exceeded hepatomegaly in frequency as an evidence of amyloidosis. It is interesting that few clinicians mention palpable spleen or liver, in view of the nearly uniform involvement of these organs at postmortem examination. Cohen [6] reports hepatomegaly in 58% and splenomegaly in 22% of his series, and Moschcowitz [4] states that the spleen is the first and most constantly involved organ. I noted unquestioned splenomegaly once.

Renal Studies

A. Results of Tests: The Urine: Albuminuria was a constant finding, usually very early in the course of the disease. The quantity fluctuated markedly from week to week or month to month. Quantity was no criterion of the severity of the renal lesion. Thirteen cases are recorded as having albuminuria in excess of 5 gm. per liter at some time. The highest amount recorded was 32 gm. per liter. Two patients yet alive had maximal proteinuria records of 15 and 25 gm. per liter, and at present show no albuminuria and normal renal function. Albuminuria in the range of 1 to 5 gm. per liter was commonly seen, but five cases never exceeded 1 gm. and two are recorded as 0.2 gm. or less per liter. Cellular elements are usually wanting or minimal, except in the presence of superimposed urinary tract infection. Casts are often numerous, mainly hyaline or granular, infrequently waxy.

Uremia: Three of this series died with marked azotemia, and a fourth, a diabetic, had a nonprotein nitrogen of 54 mg.% before death. Two of the uremics showed total proteins below 6 gm.% late in the disease; two had albuminuria constantly less than 5 gm. per liter, the others maxima of 6 gm. and 8 gm. per liter. Cholesterol did not exceed 250 mg.%, and declined below 150 in one uremic and in the diabetic. The latter was the only one to display edema.

Impairment of Renal Function, as judged primarily by fractional phenolsulfonphthalein excretion, was present in 13 of 20 cases; in one the phenolsulfonphthalein test returned to normal later. Two of the seven cases originally normal showed a subsequent decline of renal function. Random confirmation by the urea clearance or urine concentration tests was always consistent.

Hypertension of moderate grade was recorded twice, in both instances

associated with normal renal function. In all other cases blood pressure was within normal range or below.

Edema was found only occasionally, often early in the course of the disease when albuminuria was minimal. Of the nine cases in which edema is recorded, only four showed plasma protein depletion below 6 gm.% at any time, although the plasma albumin moiety was always less than 2.5 gm.%.

Hypoproteinemia below 6 gm.% was present in the three known uremics and in the diabetic with elevated nonprotein nitrogen referred to in the paragraph under *Uremia,* above. It is interesting that, of nine instances of hypoproteinemia below 6 gm.%, there were only two instances of albuminuria in excess of 5 gm. per liter, in addition to the one case of uremia referred to above in which 6 gm. per liter was found on one occasion.

Hypercholesterolemia in relation to the renal lesion is of importance. Plasma levels exceeding 250 mg.% occurred in six instances, and in four of these an associated massive albuminuria was found. In two there was an associated hypoproteinemia, but this was coupled with massive albuminuria in only one case. This case will be discussed subsequently.

B. Discussion: Although the clinical syndrome associated with renal amyloidosis is usually termed a "nephrosis," it is evident from the data presented that only one case in this series exhibited the classic tetrad of "nephrosis": massive albuminuria, hypoproteinemia, hypercholesterolemia and edema. This patient (case 1) is described below in detail as one showing reversal of amyloidosis. Moschcowitz [4] states that "the dominant clinical manifestations of generalized amyloidosis arise from involvement of the kidney." He objects, with good reason, to the term "amyloid nephrosis," pointing out that nephrosis is a symptom complex resulting from hypoproteinemia, and that clinically the renal manifestations do not fulfill the criteria for "nephrosis." He agrees with Letterer's [27] view that hyperproteinemia is characteristic of amyloidosis, but reasons that the huge losses of protein in the urine accompanying renal involvement cancel out this tendency. Along these same lines, Calvin and Goldberg [28] reasoned that the cachexia which results from the primary disease caused a lowering of the plasma cholesterol values, so that the typical hypercholesterolemia of "nephrosis" did not regularly appear in cases of amyloidosis with renal involvement.

It is evident that wide disparity of opinion exists concerning the clinical manifestations of renal amyloidosis. Leard and Jacques [29] review the literature to 1950 and report a case of their own of amyloid contracted kidney.

Most writers agree with Auerbach and Stemmerman [2] (a) that renal involvement of some degree is present in a high percentage of cases (83.1% in their material), and in other series [6, 30] 50 to 85%; (b) that renal amyloidosis is rarely isolated; (c) that Congo red retention is proportional to total amyloid deposition (particularly hepatic), so that an extensive renal lesion may exist with inconclusive Congo red test or, conversely, extensive

amyloid may be present without albuminuria;[31] (d) that hypertension is a rare complication, and (e) that no clear relation exists between the severity of the albuminuria, extent of renal lesion and the level of total plasma protein or albumin-globulin ratio. The subjects of this report confirm these observations, as well as Rosenblatt's[8] that there is no direct relation between the degree of albuminuria and edema. Whether plasma protein levels are responsible for edema, as he states, is uncertain from my data; at any rate, an incidence of edema in 50% of cases reported[5] far exceeds the findings in the group here reported.

The findings of most other authors differ radically from those of Auerbach and Stemmerman,[2] who found renal amyloidosis in about 27% of cases and almost always as a terminal event, and who state: "In most of the patients amyloidosis progressed until death from uremia resulted." Cohen[6] found 6% deaths from uremia. Dixon[7] reports that seven of 46 amyloids died of renal failure. Mark and Mosenthal[30] report 16 of 73 cases with azotemia, including 11 uremic deaths. Holten[14] reports two amyloid contracted kidneys in 27 cases. Pearlman[5] reports 11 cases with nonprotein nitrogen above 45 mg.% out of 135 cases. Noble and Major reported three deaths due to renal insufficiency in amyloidosis in a series of 11,000 autopsies. The author found three instances of renal failure in 30 cases, but the cause of death of some of the others was not known and may have been renal failure.

Concentrating power has been reported unimpaired,[14, 8] but the majority of patients in other series[5, 6, 2, 30] showed impairment of concentrating power and phenolsulfonphthalein excretion, a fact which the present study confirms.

Albuminuria was found in all my cases and is reported[7] in 92% of cases. It is stated[6] that it is the most important early sign, preceding a positive Congo red test in 35%. The wide variation in proteinuria is generally recognized.

Several authors[2, 33, 34] have emphasized the importance of osseous, enteric and pleuritic tuberculosis in the causation and rapid development of amyloidosis, especially the dominantly renal form. Rieselman[34] cites 28 cases of very rapidly developing amyloid "nephrosis" following wound osteomyelitis, and quotes others[8, 35] with similar cases. Fishberg[37] emphasizes the importance of suppurative forms of tuberculosis as a cause of amyloidosis, with an incidence of 44%. I found no striking relationship between the dominantly renal forms of amyloidosis and extrapulmonary or suppurative tuberculosis in this series. The data are incomplete, comprising eight known cases, mainly empyema, but including other types of tuberculosis, often multiple. Perhaps there were other instances in this series which were overlooked. At least two cases of rheumatoid arthritis (a supposedly rare cause of amyloidosis) were among this group.

A review of the information concerning plasma proteins derived from this study reveals these dominant characteristics: normal or elevated total plasma proteins, a tendency to hyperglobulinemia and inversion of the al-

bumin-globulin ratio, and wide variation of albuminuria, with no constant relationship to the level of total proteins or the A/G ratio. These suggest that the vicissitudes of the plasma protein fractions are the result of at least three influences, varying in severity, the net effect of which is reflected in the individual determinations. First, infection, which stimulates globulin formation, is probably responsible for hyperglobulinemia and elevation of total proteins. Second, the albuminuria with loss of serum albumin tends to lower the total proteins and reverse the albumin-globulin ratio. Third, the hepatic impairment operates to suppress total proteins, largely at the expense of the albumin fraction, but failure of globulin production also participates. Figure 1 is an attempt to illustrate these relationships.

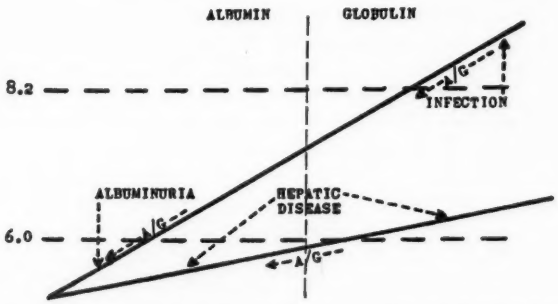

FIG. 1. The heavy lines indicate the total plasma protein level, lying largely between the normal limits of 8.2 and 6.0 gm. %. Hepatic disease is illustrated as tending to depress the T.P. line, mainly at the expense of the albumin fraction, and to shift the A/G ratio. Hyperglobulinemia resulting from infection is suggested by the upward extension of the right side of the T.P. line. The influence upon the A/G ratio is shown to be in the direction of depression. The sum of the influences depicted accounts for the characteristic plasma protein fractions in secondary amyloidosis.

DIAGNOSTIC CONSIDERATIONS

"If albuminuria and cylindruria appear in the course of advanced pulmonary tuberculosis complicated by a suppurative process, tuberculosis of serous membrane, enteritis or any other major complication of tuberculosis or in osseous tuberculosis, the diagnosis of renal amyloidosis may be entertained with the expectation that further study will confirm it. If, associated with these changes, the liver and spleen are enlarged, the diagnosis may be considered reasonably well established. If spleen and liver are not enlarged, the presence of edema, normal or low blood pressure, hyposthenuria, a normal output of dye (P.S.P.), normal N.P.N. and normal eyegrounds, support the diagnosis." [33] This quotation from Altnow and his co-workers may be taken as a good guide to the diagnosis of amyloidosis and not alone to the renal manifestations. My data differ in that a high incidence of impairment of dye (phenolsulfonphthalein) excretion was encountered. The

finding of splenomegaly was rare, and the incidence of suppurative and extrapulmonary tuberculosis not so impressive. The wide fluctuation of quantitative albuminuria was striking, as was the frequent occurrence of depressed ratio of cholesterol ester to total cholesterol as the dominant defect of hepatic function in the presence of hepatomegaly. Next to albuminuria, hepatomegaly is the most frequent sign of amyloidosis.

Regression of Amyloidosis

There were two cases of apparent regression of amyloidosis which, because of the rarity of this occurrence, are reported here in detail.

Case Reports

Case 1. A white male, aged 32 years at the time of discovery of amyloidosis, had had known tuberculosis for four years. This was complicated by empyema and a draining sinus, which persists. He had shown marked hepatomegaly and splenomegaly, now absent. Edema was severe in late 1949 but disappeared after transfusions. Today his only significant abnormalities are the cephalin flocculation test, showing 3 plus, and the cholesterol ester, total cholesterol ratio of 50%. In this patient there is seen an apparent reciprocal relationship between total protein and plasma cholesterol. This is the most characteristic "nephrotic" patient in the series. The following table summarizes the laboratory data.

Table 1

Date	7–48	8–49	1–50	6–54
Congo red	90%			40%
Total cholesterol		400	360	170
Cholesterol esters		350	185	85
Total protein	6.2	5.46	6.29	7.48
Albumin/globulin	0.65	1.08	0.92	1.55
Cephalin flocculation	0			3+
Thymol turbidity				3
Bromsulphalein	0	0–5		
Phenolsulfonphthalein		30–50	33–61	
Albuminuria	16–25	2–4	8–10	0

Albuminuria in grams per liter indicates the range for a period of months near the date. The figures for phenolsulfonphthalein excretion are percentages after 15 and 60 minutes, respectively.

Case 2. A colored female diabetic had had known tuberculosis for two years before amyloidosis was found at the age of 32 years. Hepatomegaly, grade 1, in 1949 and albuminuria, 0.2 to 0.5 gm. per liter, suggested possible amyloid. At present she is very obese and has occasional slight ankle edema. Her tuberculosis is arrested.

There has been a reversal of the Congo red test but persistent evidence of hepatic and renal lesion without decompensation.

The mild elevation of cholesterol is present with adequate total plasma proteins and serum albumin level, and is consistent with obesity and diabetes. Beardsley [3] found persistent albuminuria in the case of reversal he reported.

The following table summarizes the laboratory data.

TABLE 2

Date	9–49	5–50	6–51	9–52	6–54
Congo red	100			100	35
Total cholesterol	130	280	220		269
Cholesterol esters	20	200	115		155
Total protein	8.58	8.62	8.83	7.74	7.49
Albumin globulin	0.57	0.55	0.92	0.94	0.81
Cephalin flocculation			2+		3+
Thymol turbidity		8	9	6	6
Bromsulphalein	10	5	5–10	5	
Phenolsulfonphthalein	5–36	33–71	23–55		
Albuminuria	1–3	1–5	1–4	1–0.5	3

Albuminuria in grams per liter indicates the range for a period of months near the date. The figures for phenolsulfonphthalein excretion are percentages after 15 and 60 minutes, respectively. Nonprotein nitrogen was found constantly between 22 and 26 mg. %.

PROGNOSIS

The average duration for the whole series was 2.26 years. Of 13 cases surviving after 1951 the average was four years, and the average duration of amyloidosis in the seven cases surviving to date is five years. The introduction of streptomycin therapy in 1948 and the beginning of its intensive use in 1949, usually in combination with PAS, appear from the data to show its effects upon amyloid disease in 1950 and subsequently. Isonicotinic acid hydrazide, introduced in 1953 and given in combination with the other drugs since then, has been received by all the survivors. The duration of amyloidosis from the time of its discovery to the date of death or, in the case of the survivors, to mid-1954, is graphically demonstrated in figure 2.

Comparison with Cohen's [6] 1943 figures is interesting. He found 50% mortality in six months, 72.5% in 12 months and 88% in 24 months, whereas the author finds for the same periods rates of 23%, 37% and 50%.

This is striking evidence of the improved prognosis for amyloidosis with advances in combined surgical treatment and chemotherapy of tuberculosis. Except for the occasional case that dies of uremia, the victims of secondary

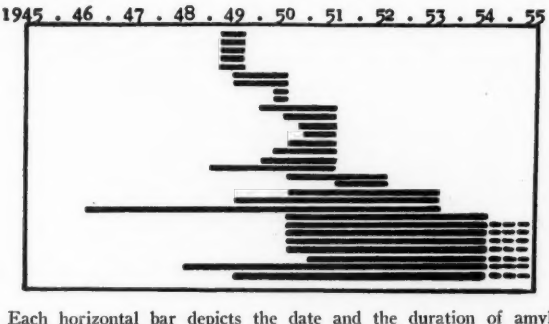

FIG. 2. Each horizontal bar depicts the date and the duration of amyloidosis from the time of its discovery to the termination in each of the 30 patients studied. The seven lowest bars are extended by broken lines representing survival to the time of writing. The improved prognosis is evident.

amyloidosis succumb to their primary disease. Extensive infiltration by amyloid may persist for long periods with minor functional impairment of involved organs.

Summary

A study of 30 cases of amyloidosis secondary to tuberculosis has revealed the following:

1. There was a marked preponderance of Caucasian males.
2. The average age of the group was 36.6 years, with a range of from 18 to 61 years.
3. Congo red retention of 90% or more was a standard criterion for diagnosis and, when absent, initially appeared late.
4. The average duration of known tuberculosis to the presumptive onset of amyloidosis was 4.6 years. The data suggest higher resistance to amyloidosis and later onset among females.
4. Albuminuria and hepatomegaly were almost always present.
6. Studies of hepatic function indicated impairment as evidenced by (a) diminished cholesterol esterification in 13 of 20 cases, (b) depression of normal albumin-globulin ratio in 21 of 28 cases, (c) cephalin flocculation of 2 plus or higher in 11 of 12 cases, (d) elevated thymol turbidity in only four of 11 cases tested, and (e) retention of Bromsulphalein above 10% in eight of 23 cases.
7. Hypercholesterolemia was found in six of 23 cases, and was associated with massive albuminuria in four instances. The presence of hypercholesterolemia offers a more favorable prognosis in some cases.
8. The alterations of total plasma protein and its fractions are the result of the net effect of the stimulation of globulin formation by infection, albumin loss by reason of albuminuria, and the depressing effect upon the production of all protein fractions by hepatic impairment.
9. Four instances of renal failure to the point of nitrogen retention were observed; three of these died in uremia.
10. Impairment of renal function as measured mainly by phenolsulfonphthalein excretion and confirmed in some instances by either urea clearance or concentration tests is present in a majority of cases. The severity of the albuminuria did not parallel impairment of renal function.
11. The classic syndrome of "nephrosis" is seldom seen in amyloidosis. Edema is absent or minimal in the majority of cases observed and, when present, does not necessarily accompany hypoproteinemia or severe albuminuria.
12. The average duration of amyloid disease for this series was 2.26 years. The average duration of 13 cases surviving past 1951 was four years, and the average duration of the seven surviving cases to date is five years. This is presented as evidence of the greatly improved prognosis for secondary amyloidosis resulting from the recent advances in the therapy of tuberculosis.

13. Cases of apparent regression of amyloidosis as judged by reversal of the Congo red retention test are reported. Evidence in these of persisting involvement of liver or kidney or both is found.

ACKNOWLEDGMENT

The author gratefully acknowledges the assistance of the clinical and laboratory staffs of the City of Chicago Municipal Tuberculosis Sanitarium, and especially the encouragement and aid of its Medical Director, Dr. Meyer R. Lichtenstein. Special thanks are also due Dr. Eli Moschcowitz, of New York City, and Dr. Harwell G. Davis, III, Director of Laboratories, the Evanston Hospital Association, for their careful review of the manuscript.

SUMMARIO IN INTERLINGUA

Le studio clinic de 30 casos de amyloidosis secundari a tuberculosis revelava un predominantia de masculos blanc. Le etates del patientes variava ab 18 a 61 annos. Le etate median esseva 36,6 annos. Le intervallo median inter le presumite declaration del tuberculosis e le detection del amyloidosis esseva estimate a 4,6 annos.

Un retention de plus que 90 pro cento de rubie congo esseva observate a un tempore o un altere in le curso pathologic de omne patientes. Albuminuria e hepatomegalia esseva presente quasi sin exception. Ambe conditiones esseva reguardate como diagnosticamente multo importante.

Esseva notate un considerabile frequentia de anormalitate hepatic. Le bases de iste observation esseva specialmente un diminuite esterification de cholesterol, un deprimite proportion de albumina-globulina, e elevate valores in le essayo a flocculation de cephalina. Altere essayos functional se revelava como anormal in certe casos. Dysfunctionamento renal con uremia non esseva commun, sed un disturbate excretion de phenolsulfonphthaleina e correspondente resultatos in altere essayos functional del renes esseva frequentissime. Le configuration classic del symptomas de "nephrosis" esseva rar. Edema esseva absente o minimal in le majoritate del casos. Quando presente, illo non se trovava in correlation con hypoproteinemia o albuminuria. Hypercholesteremia non esseva commun.

Le variationes del proteinas del plasma es apparentemente le resultato combinate del effecto stimulative del infection super le formation de globulina, del perdita de albumina via le renes, e del depression de omne fractiones proteinic in consequentia del inadequate functionamento hepatic.

Le datos indica clarmente le effecto benefic que le recente progressos in le therapia de tuberculosis ha exercite super le prognose de amyloidosis. Duo casos de apparente regression de amyloidosis con residue imperfection renal e/o hepatic es revidite in detalio.

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CASE REPORTS

TWO CASES OF PRIMARY PULMONARY HYPERTENSION WITH SUDDEN DEATH ASSOCIATED WITH THE ADMINISTRATION OF BARBITURATES *

By Scott R. Inkley, M.D., Louis Gillespie, Jr., and Robert K. Funkhouser, M.D., *Cleveland, Ohio*

The syndrome of pulmonary hypertension in the absence of apparent parenchymal lung disease or primary cardiovascular defects has been diagnosed clinically with increasing frequency since the technic of a cardiac catheterization has become widely available. The clinical picture and pathologic physiology have recently been comprehensively reviewed by Dresdale.[1] It is the purpose of this paper to report two cases which have been confirmed at autopsy, and to call attention to the untoward reaction to barbiturate anesthesia which occurred in both patients.

Case Reports

Case 1. A 41 year old white female was admitted to University Hospitals for the third time on June 13, 1952. This patient had been well until March, 1951, when she fainted while walking to her car. She was seen subsequently by a physician and treated for "nervousness." During July the patient first noted the onset of exertional dyspnea, easy fatigability, an occasional slight cough, dizziness and a nonradiating pain or pressure sensation in the epigastrium associated with exertion and occasionally followed by vomiting. In October the patient first noted swelling about her face and legs. The episodes of exertional syncope, fullness and vomiting continued. Because of abdominal fullness, a gastrointestinal series and gall-bladder x-ray were done. The patient was informed that she had a "nervous" stomach. Since exertional symptoms and edema were still present, she was digitalized and placed on a low salt diet by her private physician, following which she noted slight subjective improvement. During December a weight gain of three to six pounds occurred in spite of poor appetite and reduced activity.

The patient had had pneumonia at age 10. No history of cyanosis, dyspnea, fatigue or limitation of activity during the patient's youth was obtained. There was no history of rheumatic fever, sore throats, epistaxis or chorea. Her mother had died at age 60 of cardiac failure.

The patient was admitted to University Hospitals for the first time on December 30, 1951. Physical examination revealed a blood pressure of 110/85 mm. of Hg. Neck veins were distended in the sitting position. The lungs were clear to percussion and auscultation. Examination of the heart revealed enlargement; P_2 was split and greater than A_2. A grade I, late systolic murmur was heard throughout the precordium, best in the third and fourth intercostal spaces to the left of the sternum.

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The liver was firm, tender and nonpulsatile, and measured 20 cm. from superior to inferior border. There was slight pitting edema about the ankles and lower legs. No clubbing or cyanosis was seen.

Laboratory findings were as follows:

1. Urinalysis: specific gravity, 1.012; albumin, 0 to trace. Hemoglobin, 15 gm.; hematocrit, 46%; white blood cells, 11,000, with a normal differential. Venous pressure (antecubital vein), 105 mm. saline; on liver pressure, 120 mm. saline. Cir-

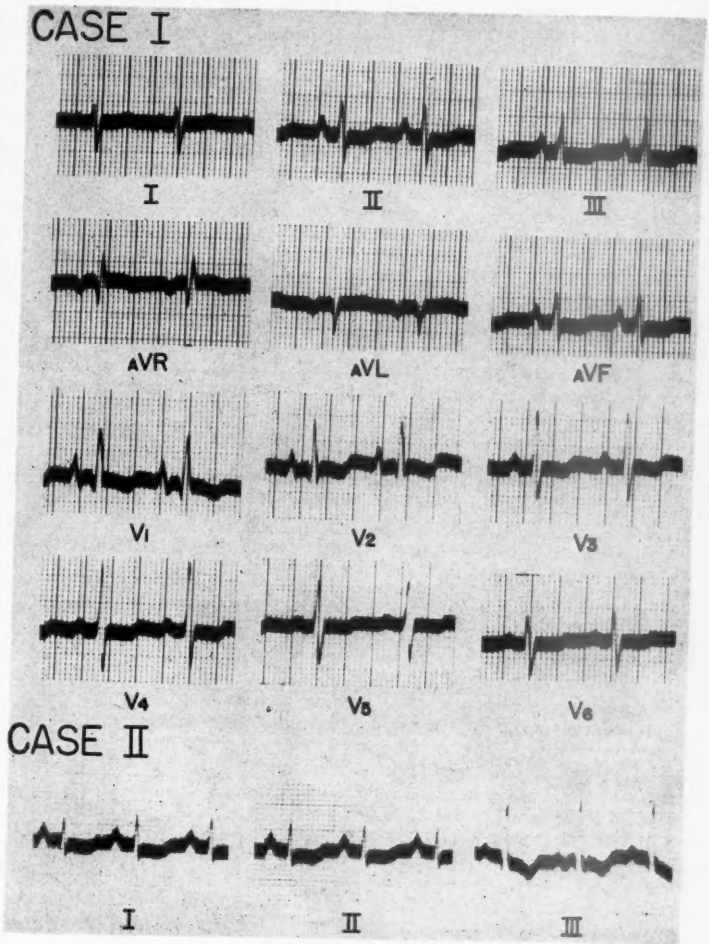

FIG. 1. Electrocardiograms from cases 1 and 2. Right ventricular hypertrophy is obvious in case 1.

TABLE 1

Results of Cardiac Catheterization Studies in Cases 1 and 2. Note the low pulmonary capillary pressure and high pulmonary artery pressure in Case 1

Case	Cardiac Output Liters/min.	Pulm. Art. Pressure Mm. Hg	Pulm. Cap. Pressure Mm. Hg	Peripheral Pressure Mm. Hg	Pulmonary Resistance Dynes sec./cm.$^{-5}$	Art. O_2 Sat'n %	Hgb. Gm./100 ml.
I	1.90	84/42	10	100/70	1087*	92.0%	15.0
II	3.46	96/53	—	107/72	—	69.0%	21.9

* Predicted: 233 dynes sec./cm.$^{-5}$ (Cournand, A.: Circulation 2: 641, 1950).

culation times: magnesium sulfate, 21 seconds; ether, 13 seconds. Vital capacity, 2.0 L. (70% of normal).

2. The electrocardiogram showed abnormal right axis deviation and peaked P waves; right ventricular hypertrophy and auricular hypertrophy were present (figure 1).

TABLE 2

Summary of Results of Maximal Tolerable Exercise at 1.7 m.p.h. on a 10° Slope. Note the drop in respiratory efficiency and rise in ventilatory equivalent during and after exercise

Determination	Resting 5 Min.	Exercise 45 Sec.	Recovery				
			1 Min.	1 Min.	2 Min.	2 Min.	2 Min.
Min. vent. L./sq. m./min. spt.*	5.65	23.57	16.09	10.61	6.40	7.46	6.37
O_2 consumption Ml./sq. m./min. spt.	168.4	525.3	359.8	227.8	214.6	200.5	166.1
O_2 debt %†			36.24	14.99	12.06	8.70	—
O_2 transport O_2 cons./sq. m./hrt. rate	1.83	4.20	2.93	2.15	2.21	2.16	1.89
Vent. equiv. (O_2) L. air/100 ml. O_2	4.5	6.3	6.3	6.3	4.2	5.0	5.3
Resp. efficiency Vol. %	2.2	1.6	1.6	1.6	2.4	2.0	1.9
Respiratory rate Breaths/min.	16	30	25	20	21	21	21
Heart rate Beats/min.	92	125	123	106	97	93	88
Blood pressure Mm. Hg	111/98	108/—	114/98	—	—	108/100	—
Fitness index §	0.36						

* Standard temperature and pressure.

† O_2 debt (%) $= \frac{\text{Recovery } O_2 \text{ cons.} - \text{control } O_2 \text{ cons.}}{\text{Control } O_2 \text{ cons.}}$

§ Bruce, R. A., et al.: Arch. Indust. Hyg. and Occupational Med. 4: 236, 1951.

3. X-ray: Chest films showed enlargement of the heart, predominantly of the right side. The shadow cast by the pulmonary artery was also prominent.

4. Cardiac catheterization was performed, and the results are recorded in table 1 (case 1).

In spite of digitalization the patient continued to have dyspnea, syncope and abdominal pain. On May 14, 1953, she was re-admitted to University Hospitals. Blood pressure was 90/70 mm. of Hg. There was minimal bilateral scleral icterus, and moist râles were heard at both lung bases. An early diastolic component was added to the original murmur, heard best in the third intercostal space to the left of the sternum. P_2 was markedly louder than A_2 and was still split. The liver descended four fingerbreadths below the costal margin and was moderately tender. Minimal edema was still present. Serum bilirubin: direct, 0.8; total, 3.0. Cephalin flocculation, 2 plus; serum cholesterol, 155 mg. %; prothrombin, 41%; venous pressure (antecubital vein), 210 mm. saline. Treadmill studies performed on the patient revealed an abnormal response (table 2). There was a large oxygen debt during the recovery stage. The systolic blood pressure failed to rise, and the ventilatory equivalent failed to decrease. The fitness index was 0.36 (normal, 13 to 22). Four days after discharge the patient was re-admitted to University Hospitals with a complaint of pain in the left leg of four days' duration. This was diagnosed as thrombophlebitis and treated with Dicumarol. During the patient's short convalescence at home prior to this last admission, heart failure had progressed, and she had had daily syncopal attacks and frequent vomiting. In the hospital the patient had two episodes of vomiting, both followed by syncope and bilateral convulsive movements of the upper extremities. The electrocardiogram showed no change from previous recordings. In view of the patient's rapidly progressing deterioration with failure on medical management, thoracic sympathectomy was considered.* The evening prior to surgery the patient was sedated with 75 mg. of Seconal orally. On the morning of surgery, following introduction of an extradural catheter at the level of the third thoracic root and intubation with an endotracheal tube, the patient was given 75 mg. of secobarbital intravenously to initiate anesthesia (figure 2). Nitrous oxide-oxygen gas anesthetic had hardly been started when, within three minutes of the secobarbital administration, the patient went into shock which, despite the administration of stimulants and 100% oxygen, proved fatal.

Autopsy Report: The heart weighed 360 gm., 23% above the upper limits of normal for the body length. The right atrium was slightly hypertrophied and dilated. The wall and papillary muscles of the right ventricle were markedly hypertrophied and moderately dilated. The pulmonary artery was slightly dilated, with a circumference of 6.3 cm. just above the pulmonic valve. There were many yellowish gray atheromatous plaques, measuring 6.5 cm. in average diameter, on the endothelial surface of the pulmonary artery. There was a mural thrombus in the right auricular appendage. The foramen ovale was closed. There was moderate dilatation of the tricuspid valve; otherwise there were no abnormalities of valves, coronary arteries or aorta.

On the cut surfaces of the lungs, vessels with diameters as small as 3 to 4 mm. stood out rigid and gaping, some with very narrow lumina. Microscopic examination of the lungs (figures 4, 5 and 6) showed the arterioles and small arteries to be the seat of severe, diffuse arteriolar sclerosis, with fibrous proliferation of the intima and muscular hypertrophy of the media. The lumina of many were very narrow and at some points completely occluded by fibrous tissue or occasionally by organizing thrombi. Reduplication of the elastic lamina was present in the walls of many of the small and medium sized arteries. There were hyaline thickening

* This operation was offered because of improvement following a unilateral sympathectomy in a similar patient of Dr. Fiorindo A. Simeone, City Hospital, Cleveland, Ohio.

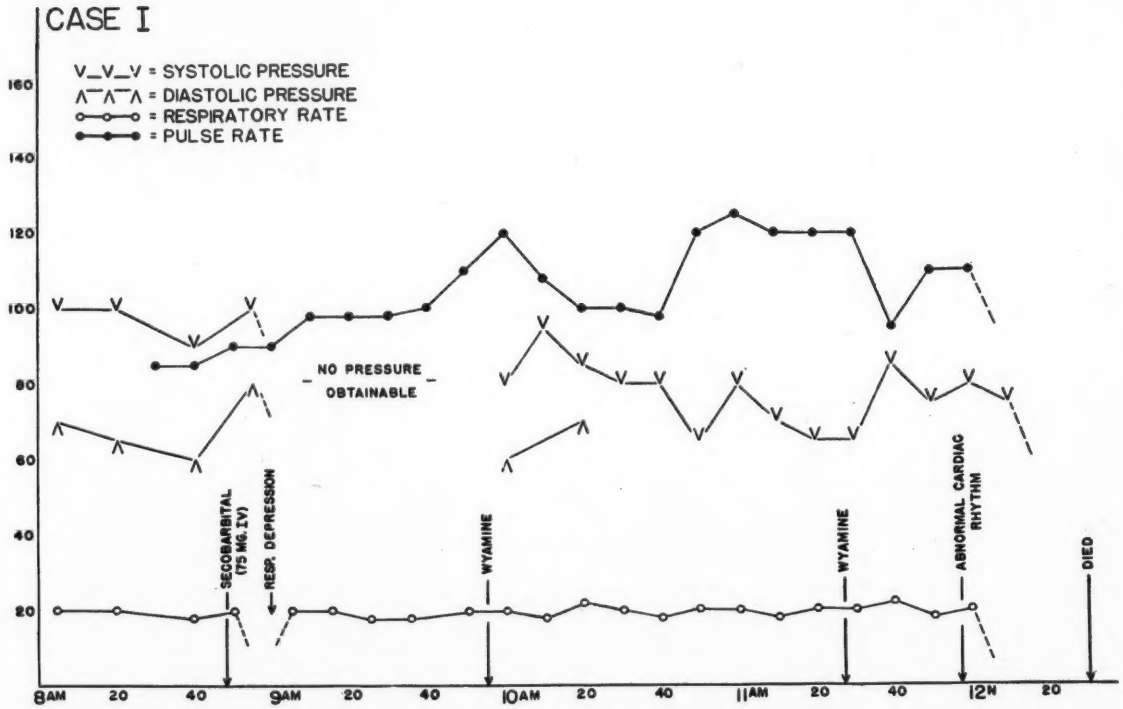

FIG. 2. Anesthesia chart for case 1, showing drop in blood pressure after secobarbital. Diastolic pressure rose only transiently with sympathetic amines.

CASE II

FIG. 2. Anesthesia chart for case 1, showing drop in blood pressure after secobarbital. Diastolic pressure rose only transiently with sympathetic amines.

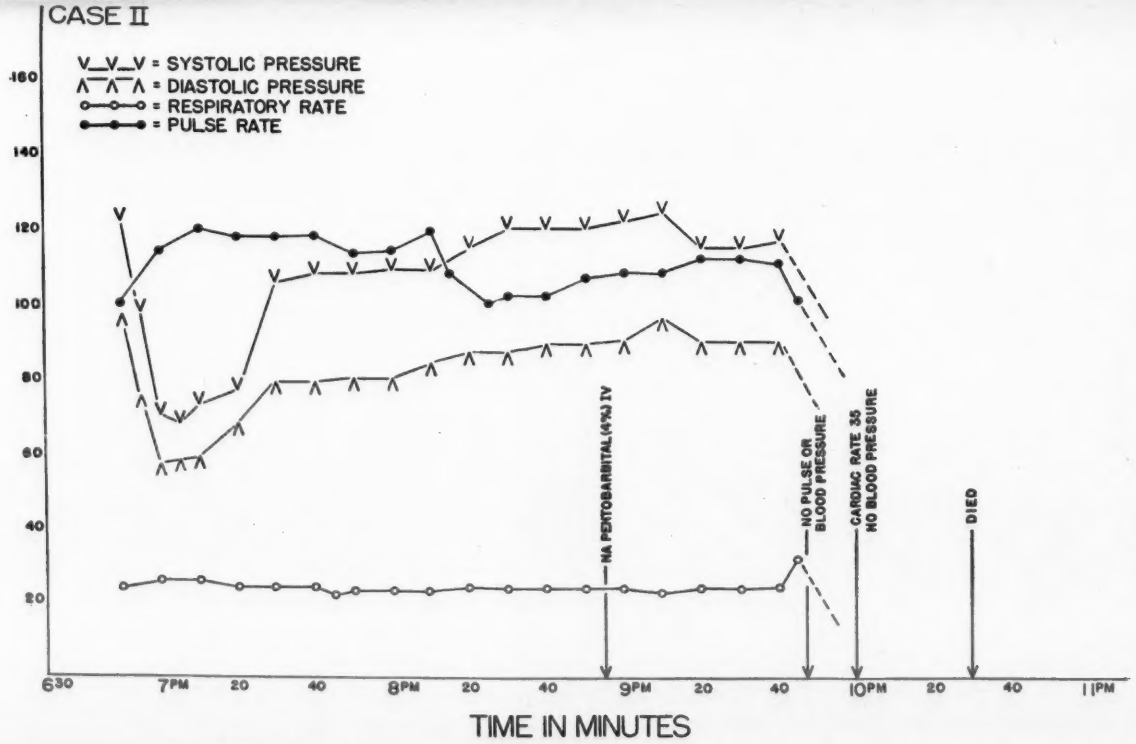

FIG. 3. Anesthesia chart for case 2. Shock appeared without significant bleeding as the wound was closed.

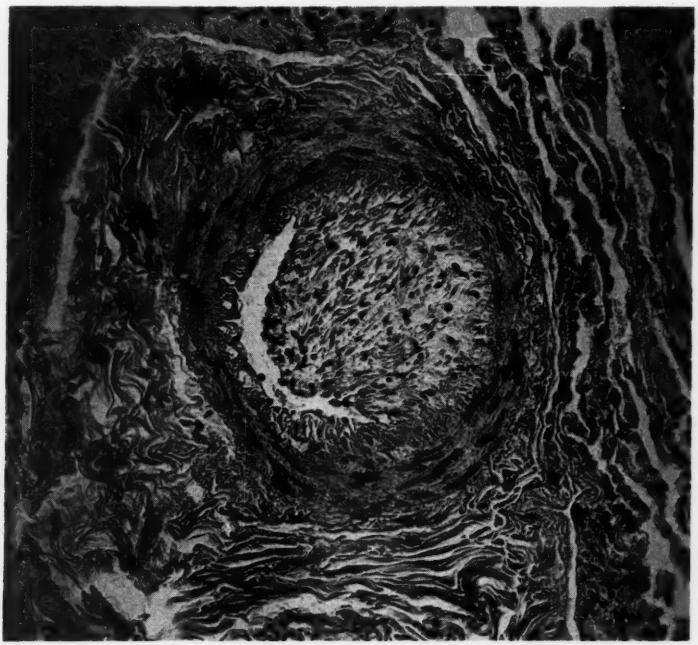

FIG. 4. Small artery showing eccentric intimal proliferation with marked narrowing of lumen. H & E stain × 215.

of many arteriolar walls and atherosclerosis of the large arteries. There was also microscopic evidence of chronic bronchitis of mild degree and of passive hyperemia of the liver and spleen, with central lobular atrophy and fibrosis of the liver.

Case 2. A 32 year old white female presented symptoms of severe cyanosis, exertional dyspnea, orthopnea and intermittent ankle edema. She had been well until the age of 26, when dyspnea followed by cyanosis gradually developed. One year prior to the onset of her symptoms she had become pregnant, subsequently aborting without any known complications. On previous physical examinations a loud diastolic murmur had been heard over the pulmonary area, obliterating P_2. Since the pulmonary artery appeared to be dilated on fluoroscopy, the murmur was believed to be due to pulmonary incompetence. Three intracardiac catheterizations were done, and the results appear in table 1 (case 2). Significant laboratory findings were as follows: hematocrit, 68%; hemoglobin, 21.9 gm.; red blood cells, 7.3 million.

On October 30, 1950, the patient was admitted to the gynecologic service at University Hospitals for treatment of low back pain. Blood pressure was 150/100 mm. of Hg. On physical examination the patient was found to be of slender build with pale skin. She was mildly dyspneic. The heart was enlarged to both the right and the left. The apex rate was 100, with no pulse deficit. A loud, apical systolic murmur and a questionable diastolic murmur were described over the apex. The pulmonic diastolic murmur was not heard. A_2 equaled P_2, and the rhythm was regular. The lungs were clear to percussion and auscultation. Abdominal ex-

amination revealed an enlarged liver, 2.5 cm. below the right costal margin, nontender. Laboratory findings on admission: Urine: specific gravity, 1.017; albumin, 4 plus; no sugar; 6 to 8 white blood cells (spun); benzidine test, negative. White blood cells, 7,000.

A laparotomy was done on October 31, and the right and part of the left ovary were removed in the process of partial dissection of a large cystic mass in the lower pelvis. The patient received spinal anesthesia—5 mg. Pontocaine and 25 mg. ephedrine sulfate—with resulting anesthesia to the level of the umbilicus. The procedure lasted one hour and was well tolerated by the patient, who returned to the ward in good condition. On November 1 the patient was operated upon again under emergency conditions for intestinal obstruction, and an end-to-end anastomosis of the colon was performed. Spinal anesthesia was again employed (figure 3)—infiltration with procaine and 25 mg. ephedrine sulfate, followed by intrathecal Pontocaine (13 mg.). The patient received Neo-synephrine, 2.5 mg. intramuscularly, following an initial fall in blood pressure. An unknown amount of 0.4% sodium pentothal was administered intravenously during the latter part of the operation (see graph), and subsequently the blood pressure and pulse became unobtainable. The patient died in spite of intracardiac adrenalin and cardiac massage.

Autopsy Report: The post mortem was limited to the thorax. The heart weighed 350 gm. The right and left ventricles were separated by the Hermann technic. The right ventricle weighed 147 gm., the left ventricle 108 gm. This indicated definite right ventricular hypertrophy. The heart was dilated, particularly the right ventricle, the right ventricular wall measuring 0.8 cm., the left 1.4 cm. The foramen ovale

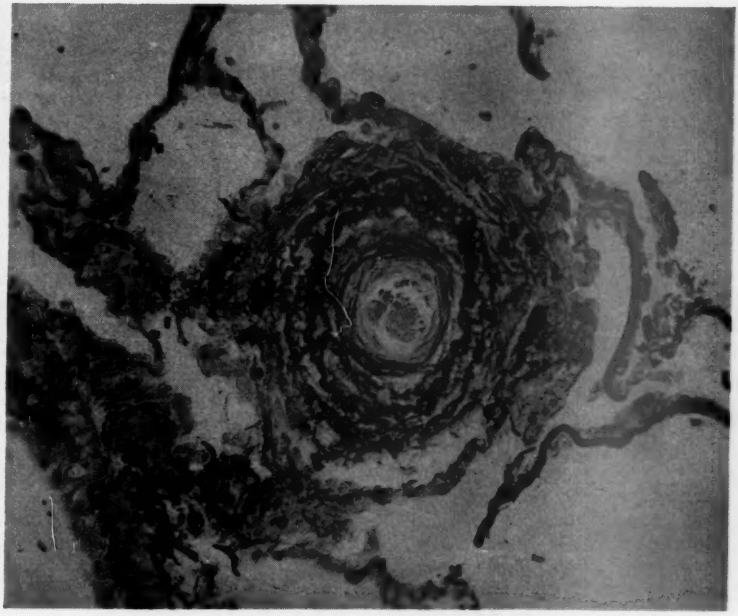

FIG. 5. Small artery showing fibrosis and elastic reduplication of wall. Elastic stain × 354.

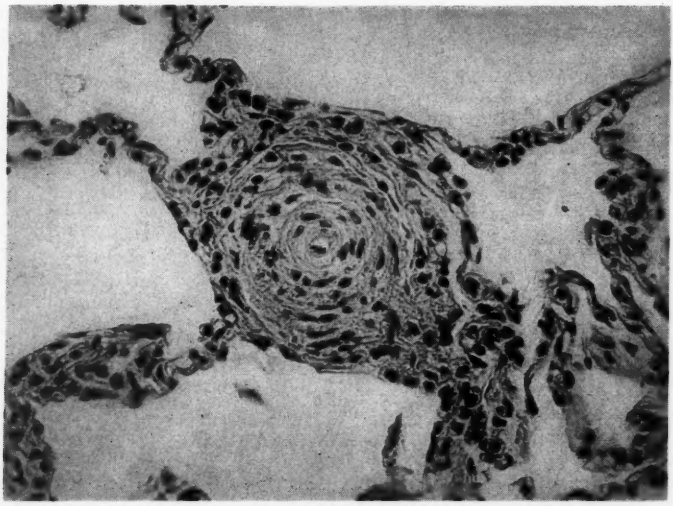

FIG. 6. Small artery showing concentric intimal proliferation, medial hypertrophy, and virtual obliteration of lumen. H & E stain × 354.

was patent (0.9 cm. in diameter). The pulmonary artery showed dilatation, and microscopic studies showed intimal hyperplasia in the arterioles. Some arteriolar lumina were occluded, others narrowed, and many were normal in diameter. The major pulmonary arteries showed moderate atherosclerosis.

DISCUSSION

It is noted that both cases had pathologic findings typical of the syndrome described as primary pulmonary hypertension. The intimal proliferation, hyalinization and thrombosis of small arterioles without evidence of involvement of lung parenchyma or capillaries are of the type described in other reports of the disease.[2, 3, 4] The clinical symptoms of weakness, easy fatigability and syncope on exertion are similar to those described by Dresdale and others; this is particularly so in case 1, where psychosomatic disease was suspected early in her course.

Both of these patients died unexpectedly, and the similarity in the mode of death suggested a possible relationship to the administration of barbiturates. It is interesting to note that case 2 had had a spinal anesthesia both the day of death and the day before without circulatory embarrassment. In this patient as well as in case 1, symptoms of shock developed shortly after the administration of small amounts of barbiturate.

In the evaluation of the relationship of barbiturate administration to the sudden death seen in both instances, the primary physiologic changes of the disease must be related to the pharmacologic effects of barbiturates. In far advanced pulmonary hypertension, one of the most striking features of the physiologic studies is the marked reduction in cardiac output. As the result

of extensive involvement of pulmonary arterioles by endothelial proliferation and thrombosis, or both, the pulmonary vascular bed is reduced and cardiac output is then found to be less than half its expected value. The exertional syncope and fatigue noted so characteristically in patients with the disease are probably the result of this restriction in resting and exertional cardiac output. When greater demands are placed on the heart during exercise, the restricted pulmonary bed prevents the normal response of increased output.

If barbiturates produce either a decrease in peripheral resistance or a decrease in cardiac output, circulatory insufficiency would be expected to ensue. The effects of barbiturate on cardiac output and peripheral resistance have shown a wide divergence of results in experimental animals. Studies in humans have shown a better agreement.

Observations by Johnson [5] on the changes in cardiac output and peripheral resistance during various types of anesthesia show that there is a decrease in peripheral resistance with spinal anesthesia in normal humans, as well as a slight drop in cardiac output. These studies were confirmed by Sancetta,[6] who also found a drop in total peripheral resistance. Johnson also noted a striking drop in cardiac output and a slight increase in peripheral resistance with barbiturate anesthesia. His patients were studied immediately prior to surgery, and artificially high control levels were doubtless obtained. Winchell [7] also studied the effect of sedative doses of sodium amytal on normals using Nickerson's technic for determining cardiac output from the ballistocardiogram. He found that there was characteristically a decrease in cardiac output and an increase in peripheral resistance. These changes would seem to be corroborated in case 2, where the patient tolerated spinal anesthesia but rapidly developed shock after the administration of barbiturate during the second operation.

The drop in blood pressure seen in these patients, regardless of whether it is primarily cardiac or peripheral in origin, could certainly reduce coronary flow to a degree sufficient to cause irreversible myocardial damage. It seems unlikely that the mechanism of death in these patients is similar to that seen following the administration of opiates or sedatives to patients with severe thoracic or lung disease. In the patient with pulmonary hypertension there is no ventilatory dysfunction and no evidence of arterial desaturation except in the presence of a patent foramen ovale, as seen in case 2. Sudden death in patients with thoracic or parenchymal lung disease has been explained on the basis of either an increase in bronchomotor tone, with subsequent marked reduction in ventilation, or depression of accessory muscles of respiration, both of which result in arterial desaturation and damage to the respiratory center.

In our cases, shock rather than respiratory depression was the cause of death. In both patients barbiturate anesthesia appears to be implicated in the rapid development of shock. It is possible that a general anesthesia of any type may well produce the same effect. Should surgical procedures be necessary in a patient with this disease, the greatest possible caution should be observed, and barbiturate or general anesthesia should be avoided in favor of local or spinal anesthesia.

ACKNOWLEDGMENT

We are indebted to Dr. Walter Pritchard for helpful criticism, and to Dr. James Reagan and Dr. Simon Koletsky for photographs of the lung sections and interpretation of the pathologic material.

SUMMARIO IN INTERLINGUA

Esseva notate in duo casos de primari hypertension pulmonar con classic constatationes pathologic que le patientes habeva morite brevemente post le administration intravenose de barbituratos. Studios de catheterisation habeva essite executate in ambe patientes, e in ambes le pression del arteria pulmonar habeva essite marcatemente elevate in stato de reposo. Le secunde caso esseva characterisate per le presentia de polycythemia. In iste caso, sanguine arterial a oxygenation incomplete se habeva disveloppate a un periodo avantiate del vita in consequentia de un patente foramine oval con derivation dextero-sinistre. In ambe patientes symptomas de fatiga esseva presente insimul con un mal-esser general del typo vidite in neurasthenia.

Le autores opina que le subitanee morte associate con le administration de barbituratos esseva possibilemente connectite con le reducite volumine cardiac e le augmentate resistentia peripheric que altere investigatores ha constatate como effecto del drogas mentionate. Il esseva postulate que un reduction additional de un jam reducite volumine cardiac pote producer ischemia con cambiamentos irreversibile del myocardio. In patientes con iste morbo il es necessari tractar le question del anesthesia con extreme precaution. Le uso de anesthesia local o spinal pare preferibile.

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PRIMARY AMYLOIDOSIS WITH SPONTANEOUS RUPTURE OF THE SPLEEN AND SUDDEN DEATH *

By JOHN F. DRAPIEWSKI, M.D., F.A.C.P., SANFORD B. STERNLIEB, M.D., and ROBERT JONES, M.D., *Wilkes-Barre, Pennsylvania*

THE first case of primary amyloidosis was reported by Wilks [1] in 1856. Ninety-six years later Higgins and Higgins [2] had gathered a total of 71 cases. Like any disease the clinical diagnosis of which depends upon a sensitive index of suspicion, primary amyloidosis is perhaps less rare than these figures indicate. Yet it is certainly not a common disease, and primary amyloidosis complicated

* Received for publication June 23, 1954.
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by spontaneous rupture of the spleen is most unusual. The first such case was reported by Wiley, Teeter and Schnabel.[3] Recently Frohner,[4] in a discussion of trauma and preëxisting disease with rupture of the spleen, did not include primary amyloidosis in his list of preëxisting diseases. The present case represents the second example of the complication and, as far as we know, the first in which death was sudden and unexpected.

Case Report

Clinical Data: A physician received imperative summons to attend a patient whom he had never seen before. He found a 52 year old white man in a profound state of shock. One-half hour before there had been sudden onset of very intense, generalized abdominal pain, followed rapidly by weakness and nausea. The patient was cold and clammy, his pulse rapid and weak, and the systolic blood pressure less than 85 mm. of mercury. He was conscious and rational. He had not vomited. Despite abdominal rigidity, the liver edge was outlined a hand's breadth below the costal margin. The man had not consulted a physician for any reason for many years. Relatives had observed that he had "looked unwell" for many months and that he apparently had lost weight. Subsequent inquiry yielded no additional historical information of significance. A tentative diagnosis of a ruptured viscus with "internal" hemorrhage was made and, following emergency treatment, he was sent to the hospital. A plasma transfusion pending crossmatching of blood was started. Despite rapid intravenous administration of this he failed very rapidly and died within 20 minutes of admission. There was an interval of approximately 90 minutes from onset of symptoms to death.

Postmortem Examination: The autopsy was performed 10 hours after death. The body was that of a well developed and well nourished man measuring 73 inches in length. The estimated weight was 210 pounds. There was no convincing evidence of recent, rapid weight loss. The axillary and chest hair was sparse and silky. There was distention of the abdomen, with a tympanitic percussion note at the crest and a flat note at the flanks. The peritoneal cavity contained 2,500 c.c. of liquid and recently clotted blood. There were a few fresh clots, with abundant pooling of blood in the left upper quadrant. The spleen (figures 1 and 2) weighed 800 gm. It was a mottled blue-red, smooth, distinctly soft and friable organ. To the left of the notch immediately inferior to the rounded edges there was a perforation of the capsule with excavation of the underlying splenic substance. This measured 2.5 cm. in diameter and had ragged, irregular margins. The cut surfaces were dusky red and revealed a "honeycomb" pattern of the pulp, the cavities of which were occupied by fresh, liquid blood. There was very extensive subcapsular hemorrhage. The liver weighed 5,200 gm. It was a mottled yellow-brown, smooth, dense and very firm and fibrous. There were gentle undulating elevations of the surface. The cut surfaces were tan with a gray cast, smooth and homogeneous, and had a tough, resilient character. The adrenal glands together weighed 18 gm. Their gross appearance was not remarkable. Each kidney weighed 180 gm. Macroscopically there was no significant departure from normal. The heart weighed 500 gm. The epicardial fat was increased in amount. The myocardium was pale and flabby. There was a mild degree of coronary arteriosclerosis. The cardiac measurements were within normal limits. All other abdominal and thoracic viscera, the genitalia and the lymph nodes were grossly unremarkable. The central nervous system and the tongue were not examined.

Significant microscopic abnormalities were limited to the spleen, liver and adrenal glands. Sections of formalin-fixed sections stained with hematoxylin and eosin showed almost total alteration of the lobular architecture of normal liver. Cords of liver cells were rather sparsely distributed throughout a pale pink, smooth, acellular,

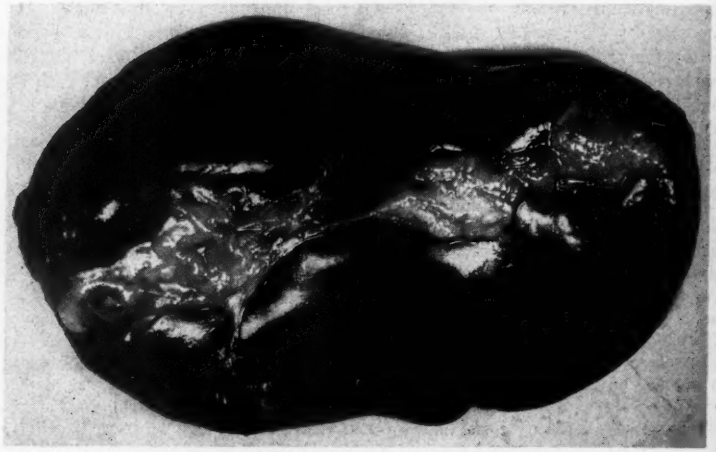

FIG. 1. Inferior surface of spleen showing the point of rupture.

hyaline-like matrix (figure 3). The microscopic structure of the spleen (figure 4) was so changed as to be unrecognizable had it not been for the persistence of trabeculae and capsule. There were homogeneous, pale pink substance similar to that observed in the liver, freshly extravasated blood and a few small round cells indistinguishable from lymphocytes. Distributed throughout were small clefts and spaces filled with blood. The structure of the adrenal glands was similarly obscured by deposits of amyloid.

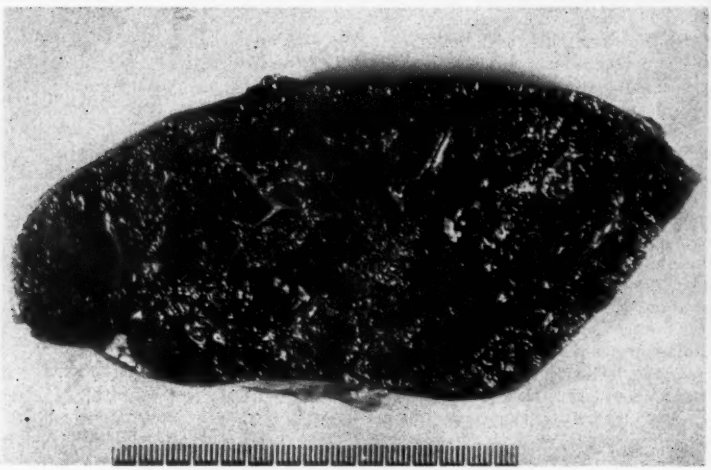

FIG. 2. The cut surface of the spleen.

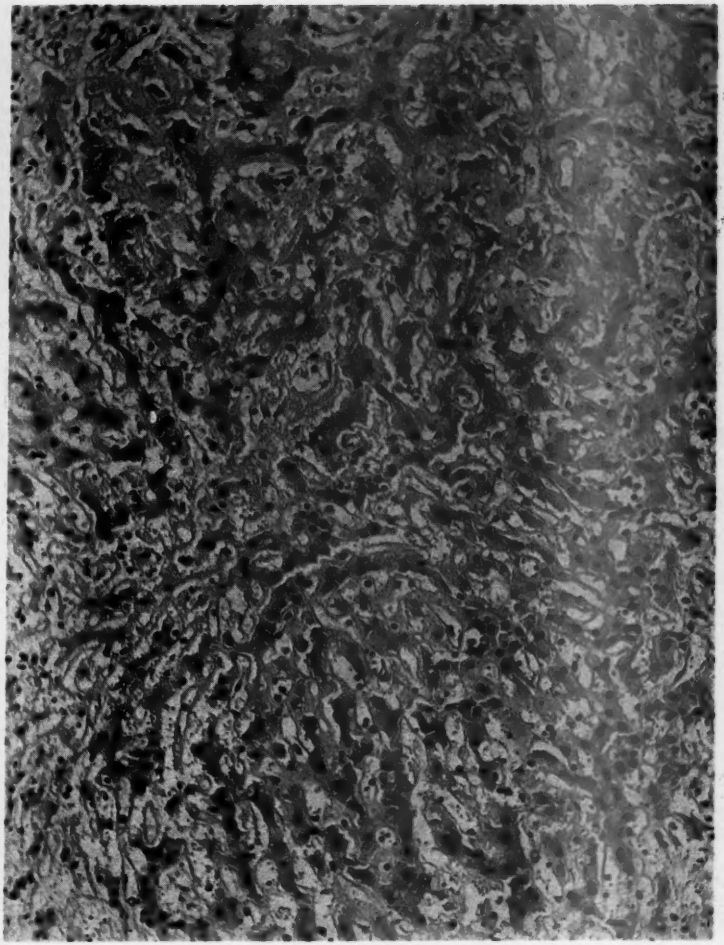

FIG. 3. Liver. Hematoxylin and eosin. × 125.

FIG. 4. Spleen. Hematoxylin and eosin. × 125.

The tissue was subjected to the reaction of crystal violet, Congo red and the van Gieson stains. The latter was used following the suggestion of Dahlin, Stauffer and Mann.[5] Only crystal violet demonstrated a satisfactory metachromatic response in liver, spleen and adrenal glands. The arterioles of other organs demonstrated smudges of color which probably represented amyloid, but the changes were not striking. Sections of heart and nerve disclosed no convincing evidence of amyloid. The bone marrow showed normoblastic erythropoiesis, and there were no abnormal cells.

Pathologic Diagnosis: In the absence of suppurative disease, multiple myeloma, the stigmata of syphilis, etc., a diagnosis of primary amyloidosis with atypical distribution and spontaneous rupture of the spleen was made.

Discussion

The absence of evidence of any preëxisting disease which might conceivably have played an etiologic role constituted the basis for classification of this case of amyloidosis as primary. It is generally accepted that secondary amyloid typically involves the parenchymatous organs, in contrast to the predilection of primary amyloid for tissue of mesenchymal origin. However, as stated by Whittlesey[6] and Dahlin,[7] there is so much overlapping that anatomic distribution cannot serve as a satisfactory basis for differentiation. The third point of difference—atypical reactions of primary amyloid to some of the metachromatic stains—is, in our somewhat limited experience with the disease, a nebulous basis for distinguishing the varieties of amyloidosis. This is based upon the lack of uniformity of reaction, at least in our hands, of classic secondary amyloid to many of the metachromatic stains.

The correct diagnosis, of course, was not made clinically in this case, nor was it made at the autopsy table. The soft, friable character of the spleen did not suggest amyloid. It remained for the sections to disclose the true nature of the disease. A plea has been made for the premortem diagnosis of primary amyloidosis.[8] The clinical manifestations of the disorder are protean and lack distinctiveness. It would appear that, except in those instances where a visible abnormality suggests biopsy (as in the skin), the diagnosis must be one of exclusion conditioned by a high index of suspicion. It is then that the diagnostic procedures of definitive value may be employed.

Fig. 4. Spleen. Hematoxylin and eosin. × 125.

Summary

A case is reported of primary amyloidosis in which death was suddenly precipitated by spontaneous rupture of the spleen with massive hemoperitoneum. The distribution of the amyloid was atypical, and there was a paucity of symptoms and signs. Unexplained heart failure (a feature of primary amyloidosis emphasized by Wiley et al.[3]), which might have suggested the diagnosis, was not present.

Summario in Interlingua

Amyloidosis con ruptura spontanee del splen es rar. Solmente 2 tal casos ha previemente essite reportate. Le presente reporto concerne un homine de 52 annos de etate qui habeva habite nulle previe affection sed qui habeva monstrate "un aere indisponite" durante plure menses. Subitemente ille experientiava sever dolores abdominal e demonstrava le signos de un "acute abdomine chirurgic." Ille moriva intra

90 minutas. Le autopsia constatava hemoperitoneo e morbo amyloide afficiente hepate, glandulas adrenal, e splen, con ruptura de iste ultime. In le absentia de signos de pre-existente morbos, le amyloidosis esseva classificate como primari.

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SICKLE CELL–HEMOGLOBIN C DISEASE *

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Recent studies have shown that sickle hemoglobin can be differentiated electrophoretically from normal adult hemoglobin,[1, 2] and have also demonstrated the existence of a new abnormal hemoglobin, which has been designated as hemoglobin C.[3, 4] It has been shown further that hemoglobin C, like sickle cell hemoglobin, is a hereditary abnormality. Its inheritance is as a Mendelian dominant. Homozygous hemoglobin C produces a mild hemolytic anemia and an increase in target cells in the peripheral blood. Cases have been described by Spaet, Alway and Ward,[9] Ranney, Larsen and McCormack,[6] and Watson.[10] The trait for hemoglobin C produces no symptoms. All cases reported to date (April, 1954) have been in individuals of the Negro race.

In the studies of Smith and Conley,[5] 500 Negroes were surveyed by electrophoretic methods. The incidence of sickle hemoglobin they found was 8.4%, and that of hemoglobin C was 2%. When the traits for sickling and hemoglobin C appear in the same individual, the disease entity known as sickle cell-hemoglobin C disease is produced. This is the genetic composition of the patient illustrated, and the disease to be discussed in this report.

Case Report

A 51 year old Negro male was first seen at the New York Hospital in February, 1954, with the chief complaint of right leg pain of three weeks' duration.

* Received for publication June 29, 1954.
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He had enjoyed excellent health until eight months before his admission to the hospital, when he was attacked by a thief, received several knife wounds and required a blood transfusion. Following this accident he developed severe aches and pains limited to the right side of his body, which finally brought him to the New York Hospital. He gave no history of previous arthralgias, growing pains, icterus, anemia or hematuria. The diagnosis of a disease with hemoglobin C was suspected when the admitting physician, Dr. Thomas Killip, noted many target cells on the peripheral blood film. It was this finding that initiated electrophoretic studies of the patient's hemoglobin.

Family history revealed that both parents were deceased, with the causes of their death unknown. Two brothers, ages 53 and 49, were alive and well. The patient was intermediate in height and weight as compared with his brothers. There were six children between the ages of 23 and nine years, and one grandchild, age one year, all in good health. There was no family history of anemia, arthralgias or underdevelopment.

Physical examination revealed a small, compactly built Negro male, complaining of severe right lower back and right leg pain. He walked slowly, dragging his right leg. Scars of the recent injury were noted on his right cheek and right shoulder. His arms, hands and skull were normal in appearance. His heart was not enlarged, but there was a blowing, grade II systolic murmur along the left sternal border. The lungs were clear. The abdominal examination revealed no palpable masses or organs. There was inconstant pain on straight leg raising of the right lower extremity. Neurologic examination was unremarkable save for slight hypesthesia and hypalgesia on the entire right side of the body.

Laboratory investigations revealed the following data: The hemoglobin was 12.0 gm. %. The hematocrit was 35%. The red blood cell count was 4.0 million per cubic millimeter. The white blood cell count was 9,300 per cubic millimeter. The differential count and platelet estimation were within normal limits. There were anisocytosis, moderate poikilocytosis and polychromatophilia of the erythrocytes. Eighty-five per cent of the erythrocytes were target forms (figure 1). Indices revealed a mean corpuscular volume of 88 cubic micra, a mean corpuscular hemoglobin of 30 micromicrograms, and a mean corpuscular hemoglobin concentration of 33%. The erythrocyte sedimentation rate was 5 mm. per hour, corrected. Hypotonic saline test revealed a marked increase in resistance of the patient's cells to hemolysis with hypotonic saline. Sternal marrow aspiration showed a normocellular marrow with a total count of 80,000 nucleated cells per cubic millimeter, with a myeloid-erythroid ratio of 1:1. Serum iron and latent iron binding capacity were normal, with values of 110 and 200 gamma, respectively. Urinalysis, Mazzini test, blood urea nitrogen, serum calcium, phosphorus, bilirubin, protein with albumin/globulin ratio as well as spinal fluid pressure, protein and Wassermann test were all within normal limits. The alkaline phosphatase of the serum was 9.4 and 8.2 Bodansky units on two occasions, the normal for our laboratory being 2 to 4 units. Sickle preparation with sodium metabisulfite was positive within 20 minutes. Filter paper electrophoresis of the patient's hemoglobin showed a combination of sickle hemoglobin plus hemoglobin C in approximately equal amounts.

X-ray studies revealed the following changes:

1. Patchy sclerosis of bones of pelvis, long bones of extremities and of carpal bones.

2. Vertebral body changes secondary to marrow proliferation and softening with bowing of end plates due to disc pressure.

3. Skull showed slight widening of diploic spaces and some demineralization of mandible.

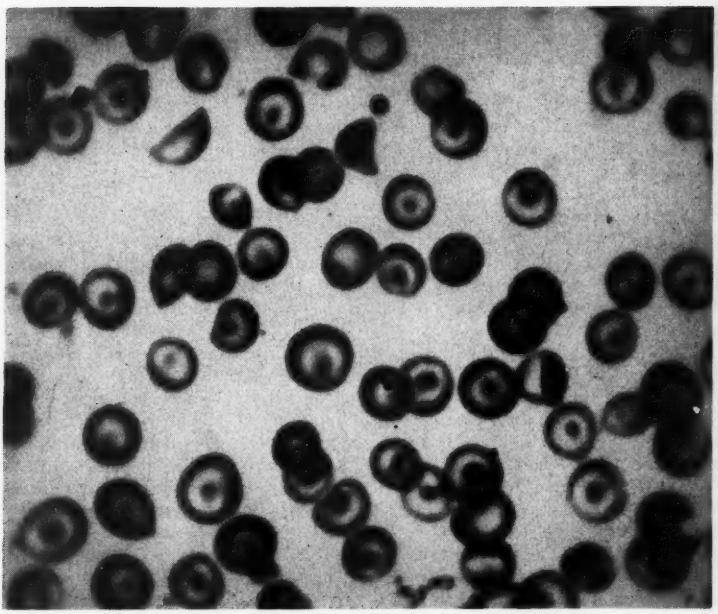

FIG. 1. Peripheral blood film, patient W. W.

4. Chest showed a diffuse sclerotic process of ribs and shoulder girdle as well as bilateral cervical ribs. The heart and lungs were within normal limits.

These changes are considered to be like those heretofore described in sickle cell disease of adults.[7, 8]

The patient's course was of interest. The symptoms which had brought him to the hospital disappeared dramatically after a lumbar puncture. It was felt that most probably they were on a functional basis and not due to his hematologic disorder, in spite of his relatively low normal hemoglobin and red blood cell values, nor to any neurologic or bone disease, although x-ray abnormalities of the skeleton were present. The patient has been well and working an eight hour day, and has had no recurrence of the abovementioned symptoms for a two month follow-up period. The diagnosis in this case is sickle cell-hemoglobin C disease.

Family Studies: Studies of the patient's family are summarized in figure 2 and table 1. He has two siblings, one of whom has been studied and found to have the sickle cell trait. His wife has no abnormality of hemoglobin. Five of his six children have been studied. All are asymptomatic. Filter paper electrophoresis shows three of the offspring to have hemoglobin C trait (i.e., hemoglobin C plus normal adult hemoglobin), and two of the offspring have sickle cell traits (i.e., sickle hemoglobin plus normal adult hemoglobin). Sickling, by the metabisulfite method, was demonstrated only in the patient, his brother, and his offspring with the sickle cell trait. The patient demonstrated more rapid sickling and a greater number of sickled cells than did his offspring with the sickle cell trait. This is

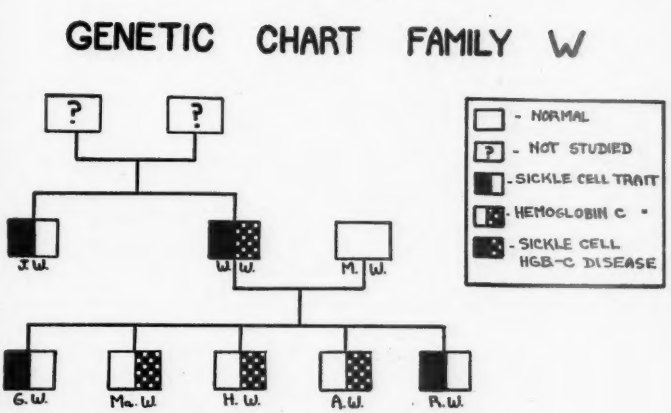

FIG. 2. Genetic chart, Family W.

probably related to the larger percentage of sickle hemoglobin in the patient's blood as demonstrated with electrophoresis. A slight hypochromic anemia was found in one daughter and is being studied further at the present time. Previous cases of the hemoglobin C trait described have shown no abnormalities in blood counts, and some have shown increase in target cells on the peripheral blood film.

TABLE 1

Summary of Hematologic Data, Family W

Individual	Age	Designation	Disease	Electrophoretic Findings	Hemoglobin in Gm. %	Hematocrit in %
W. W.	50	Patient	Sickle cell-hemoglobin C disease	Sickle hemoglobin + hemoglobin C	12.0	35
M. W.	48	Wife	None	Normal adult hemoglobin 100%	14.0	41
J. W.	52	Brother	Sickle cell trait	Sickle hemoglobin + normal adult hemoglobin	13.0	41
G. W.	23	Son	Sickle cell trait	Sickle hemoglobin + normal adult hemoglobin	14.0	41
Ma. W.	19	Daughter	Hemoglobin C trait	Hemoglobin C + normal adult hgb.	12.9	37
H. W.	17	Son	Hemoglobin C trait	Hemoglobin C + normal adult hemoglobin	15.0	
A. W.	14	Daughter	Hemoglobin C trait	Hemoglobin C + normal adult hemoglobin	10.5	38
R. W.	9	Daughter	Sickle cell trait	Sickle hemoglobin + normal adult hemoglobin	11.5	39

TABLE 1—*Continued*

Individual	Age	Designation	White Blood Count and Differential	Sickling	% Target Cells	Blood Film
W. W.	50	Patient	Normal	Yes	50–80	Normochromic Anisocytosis Poikilocytosis
M. W.	48	Wife	Normal	No	4	Normochromic Normocytic
J. W.	52	Brother	Normal	Yes—delayed	20	Normochromic Normocytic
G. W.	23	Son	Normal	Yes—delayed	2	Normochromic Normocytic
Ma. W.	19	Daughter	Normal	No	11	Normochromic Normocytic
H. W.	17	Son	Normal	No	6	Normochromic Normocytic
A. W.	14	Daughter	Normal	No	13	Slight hypochromia Slight anisocytosis
R. W.	9	Daughter	Normal	Yes—delayed	3	Normochromic Slight poikilocytosis

DISCUSSION

Review of 19 patients with sickle cell-hemoglobin C disease reported in the literature,[3–6] and comparison of them with our patient, revealed several interesting points.

Racial background, normal growth and development, the presence of a moderate normocytic anemia, the high percentage of target cells in the peripheral blood film, the demonstration of sickling, the decreased osmotic fragility and the characteristic pattern with electrophoresis were factors held in common by the patient here reported and those reviewed. The majority of the 19 patients in the literature had also recurrent arthralgias and mild hemolytic crises, as well as splenomegaly. The subject of this case report did not demonstrate these findings. None of the patients reviewed showed the roentgen changes in the skeleton here described, nor did they show an asymptomatic course, as did our patient.

Study of this family shows that the patient transmits either the gene for hemoglobin C or the gene for sickle hemoglobin to his offspring, who also inherit a gene for normal hemoglobin from their mother. The offspring therefore show the asymptomatic traits for hemoglobin C and sickling. This indicates that the genes for hemoglobin C and sickle hemoglobin may occupy the same locus on the chromosome, a phenomenon which has been called allelomorphism, or nearly the same locus which has been called close linkage. Either property would make it impossible for an individual with sickle cell-hemoglobin C disease when mated to a normal individual to have offspring with both abnormal hemoglobins. Such mechanisms would, however, insure the inheritance by each offspring of one or the other of the genes for abnormal hemoglobin.

Sickle cell-hemoglobin C disease is an inherited hemolytic disease of mild to moderate severity. The frequent appearance of arthralgias and joint swellings, as well as the occasional occurrence of cardiac murmurs, makes this disease, and also sickle cell disease, ones that may be confused with acute rheumatic fever in Negro children.

Our patient illustrates the fact (not brought out by previous studies) that this disorder can be completely asymptomatic, and should be considered in the differential diagnosis of mild anemia and bone disease in individuals of the Negro race.

Summary

1. A case is reported of sickle cell-hemoglobin C disease in a 50 year old Negro male who has been essentially asymptomatic throughout life. Striking x-ray changes of the bones are demonstrated.

2. Studies of the patient's family illustrate some aspects of the inheritance of the abnormal hemoglobins.

3. A brief review is made of 19 cases of sickle cell-hemoglobin C disease reported in the literature.

Summario in Interlingua

Es reportate un caso de morbo a cellulas falciforme plus hemoglobina C in un negro adulte. Le aspectos interessante del caso es: curso asymptomatic; examine physic normal; e constatationes laboratorial de leve anemia, alte procentage de cellulas sanguinee a forma de oculo de perdice, augmentate resistentia a hemolyse per hypotonico salin, alterationes roentgenologic de natura sclerotic in le ossos longe e le costas, e migration de character diagnosticamente anormal del hemoglobina in studios electrophoretic a papiro de filtrage.

Contos sanguinee e examines electrophoretic del hemoglobina esseva executate in altere membros del mesme familia. Iste studios monstrava que le uxor del patiente habeva normal hemoglobina adulte. Le prole de iste parentes (matre normal e patre con morbo a cellulas falciforme plus hemoglobina C) habeva combinationes de normal hemoglobina adulte con o hemoglobina de cellulas falciforme o hemoglobina C. Omne iste individuos se trovava in bon stato de sanitate. Le presente studio familial signala certe aspectos genetic de iste hemoglobinas anormal.

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COARCTATION OF THE ABDOMINAL AORTA WITH DEATH FROM RUPTURE OF AN ANEURYSM OF A CEREBRAL ARTERY *

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Introduction

The so-called "adult type" of coarctation of the thoracic aorta is a relatively uncommon congenital abnormality. The incidence of this condition has been reported by Reifenstein, Levine and Gross [1] as being one in every 3,000 autopsies. The association of this disorder with rupture of a cerebral artery aneurysm in the same individual has been well recognized and was recently documented by Wright.[2]

Coarctation of the abdominal aorta is an extremely rare condition. This is the second case to be reported of the simultaneous occurrence of a coarctation of the abdominal aorta with a cerebral artery aneurysm, and the first case in which death resulted from rupture of the cerebral aneurysm.

Case Report

A 77 year old bartender who had no known history of hypertension was in good health until July 17, 1953. At that time he had a sudden headache followed by dizziness but without loss of consciousness. He was then admitted to a local hospital by his physician. A few hours later he developed stiffness of the neck and felt nauseated. There were no localizing neurologic signs. A lumbar puncture revealed bloody spinal fluid. During the next seven days his condition improved and the spinal fluid cleared. However, in the following three days the spinal fluid became increasingly bloody. He had several generalized convulsions and lapsed into coma. A tracheotomy was done because of respiratory distress. On July 27 he was seen for the first time by one of us (J. W. M.) in consultation, and bilateral papilledema was noted, greater on the left. A left carotid arteriogram was then done, revealing a saccular aneurysm of the left anterior cerebral artery (figure 1). Because of the serious condition of the patient, the right lateral ventricle was tapped to lower intracranial pressure. The ventricular fluid was grossly bloody and under increased pressure. An attempt to tap the left lateral ventricle was unsuccessful. The patient was transferred to the San Jose Hospital on July 28.

Physical examination on arrival revealed a comatose elderly male with stertorous

* Received for publication July 6, 1954.

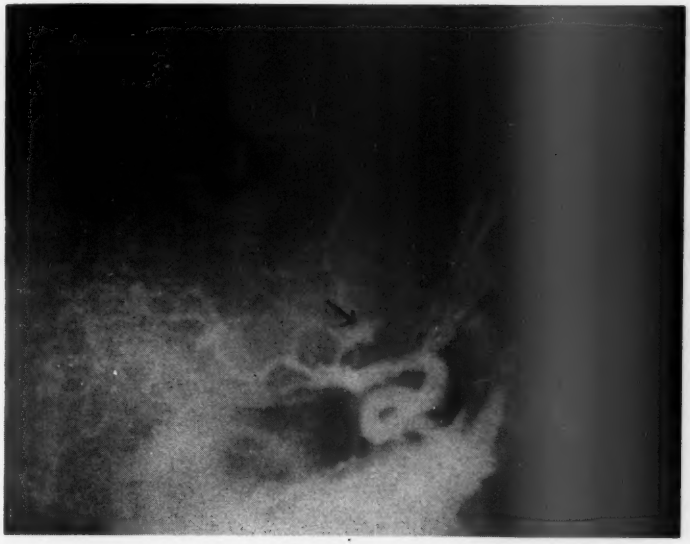

FIG. 1. Arteriogram showing aneurysm (see arrow) arising from the left anterior cerebral artery.

respirations. His rectal temperature was 100.2° F.; pulse, 76 per minute with occasional irregularities; respirations, 30 per minute; blood pressure, 160/100 mm. Hg. The pupils were small, equal and fixed. There was bilateral papilledema, greater on the left. No hemorrhages or exudates were seen. Nuchal rigidity was present. The heart was enlarged to the left, tones were of good quality and no murmurs were heard. There were a few pulmonary rhonchi over all lung fields. The abdomen was soft and no masses or organs were felt. The peripheral arteries were beady and sclerotic. The dorsalis pedis and posterior tibial pulses were all palpable. The deep tendon reflexes were brisk and equal, and no pathologic plantar reflexes were elicited. All extremities moved in response to painful stimuli.

Laboratory studies revealed a red blood count of 5,000,000 per cubic millimeter; hemoglobin, 97% (15.5 gm. %); white blood count, 15,800 per cubic millimeter. Differential count showed 69% segmented forms, 14% stabs, 11% monocytes and 6% lymphocytes. Urinalysis revealed a specific gravity of 1.006, a slight trace of albumin, the absence of sugar and acetone, 5 white blood cells per high power field, 15 to 20 red blood cells per high power field, and an occasional hyaline cast. The blood nonprotein nitrogen was 59 mg. % and the fasting blood sugar was 109 mg. %. A portable chest x-ray was negative except for prominence of the left ventricle and sclerosis and tortuosity of the aorta. There was no erosion of the ribs. An electrocardiogram revealed regular sinus rhythm with occasional premature ventricular contractions.

Shortly after his arrival at the hospital the right lateral ventricle was tapped again and much bloody fluid under moderate pressure was released. X-rays taken of the skull after the injection of 20 c.c. of air revealed filling of the right occipital and temporal horns only. No air entered the third or left lateral ventricles or the right frontal horn. These findings were interpreted as evidence of extensive intra-

ventricular hemorrhage with clot formation. Specific surgical treatment of the aneurysm was considered pending improvement in his general condition.

In spite of supportive therapy his condition became worse. The blood pressure showed wide fluctuations, ranging from 160/100 mm. Hg to 270/160 mm. Hg. During the next five days the patient's condition deteriorated. Cheyne-Stokes respirations developed, he vomited coffee-ground material, and terminally the temperature rose to 105° F. He died on August 3, and an autopsy was performed.

The significant autopsy findings were limited to the brain and the aorta. There was a thin-walled saccular aneurysm measuring 3 by 4 by 2 mm. arising from the left anterior cerebral artery 7 mm. distal to the anterior communicating artery (figure 2). The apex of the sac was replaced by a recent clot which was continuous with a much larger coagulum extending into the left frontal lobe. The hemorrhage had destroyed a large portion of the left frontal lobe and ruptured into the left frontal horn. The left lateral ventricle was entirely filled with a recent clot which extended into the third and fourth ventricles. There were numerous yellow plaques on the vessels of the circle of Willis.

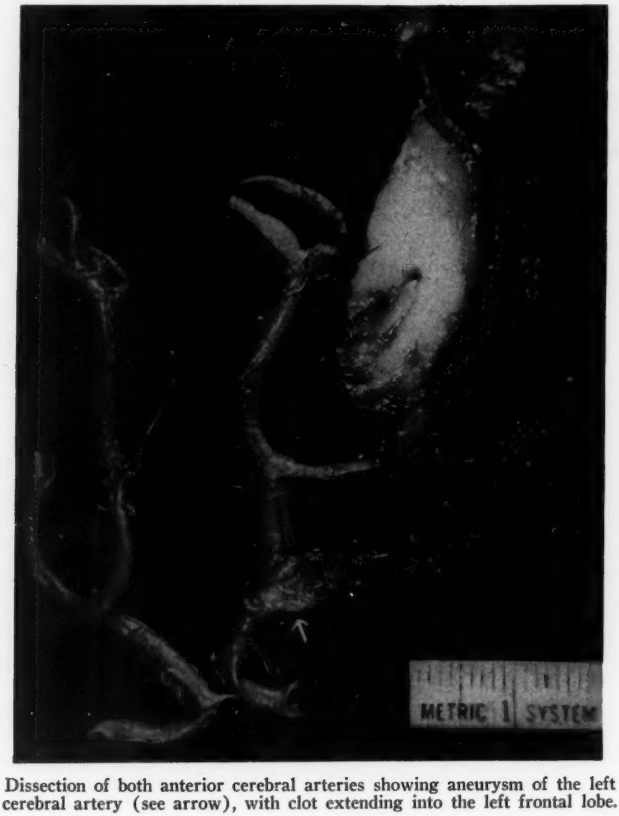

FIG. 2. Dissection of both anterior cerebral arteries showing aneurysm of the left anterior cerebral artery (see arrow), with clot extending into the left frontal lobe.

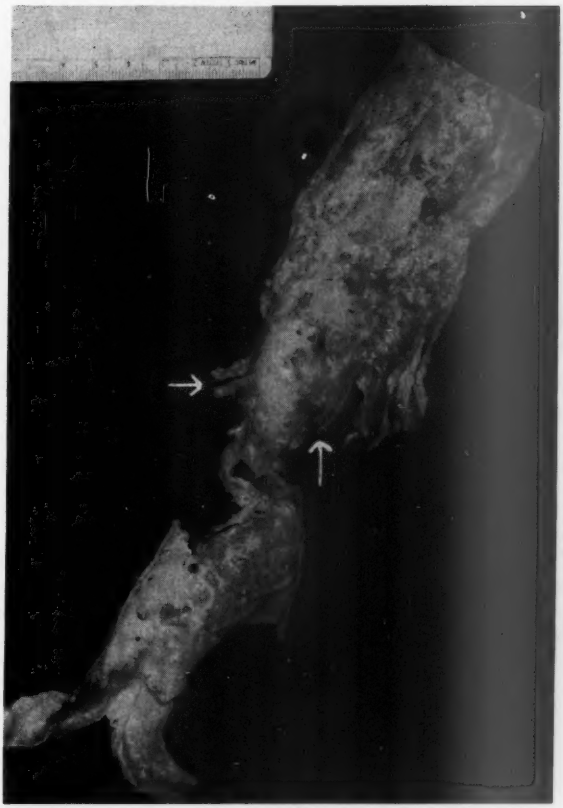

FIG. 3. Coarctation of the abdominal aorta commencing immediately below the level of the renal arteries (see arrows).

The aorta was extensively involved with atheromatous plaques, of both the calcified and the ulcerative types. Very little unaffected intima remained between these plaques. Generally, the diameter of the aorta was diffusely increased, with a circumference measuring up to 8 cm. down to a point 7 cm. above the bifurcation of the aorta. At this point the aorta was gradually reduced to a diameter of approximately 5 mm. and a circumference of 1.6 cm. (figure 3). At the site of coarctation it was markedly tortuous, and assumed an S form directed first to the right and then to the left. The narrowed area involved approximately 4 cm. of the aorta; it commenced at a point immediately below the level of the renal arteries and extended to the inferior mesenteric artery. Beyond the area of contraction the circumference gradually increased to 5 cm., and the common iliac arteries were of uniform diameter. The heart weighed 350 gm., and there was no significant hypertrophy of the left ventricle.

Discussion

The great majority of cases of coarctation of the aorta are differentiated by Taussig [3] into two separate groups. The first is the so-called "infantile type," in which the narrowing is diffuse in the arch of the aorta and is usually found between the left subclavian artery and the ductus arteriosus. This type is nearly always associated with cardiac defects and is hardly ever compatible with life for more than a few weeks. The second is the so-called "adult type," and here the coarctation is localized at or just above the ductus arteriosus, which is usually partially or totally obliterated. These patients usually show no other significant cardiac abnormality except, occasionally, a bicuspid aortic valve. They usually survive to adult life and are candidates for excisional surgery of their coarctation.

A relatively small number of cases of coarctation of the aorta have been described in which the area of stenosis is below the region of the ductus arteriosus. This group of cases is best subdivided into two separate types on the basis of location, appearance, and probably different etiology.

The first type exists when the coarctation is above or at the level of the diaphragm.[4–13] Here there is always a diffuse, elongated narrowing with evidence of periaortic fibrosis suggestive of an acquired condition. Hasler [5] felt that this type of narrowing resulted from an organized thrombus of unknown origin and localized inflammation. Nine of the 10 cases of this type reported occurred in young women. Six [7, 8, 10, 11, 12, 13] cases underwent surgery, and in three [10, 11, 13] of these the narrow segment was successfully resected and replaced with a preserved aortic homograft. In two cases [7, 8] an adequate aortic graft was not available. Glenn [12] had a patient with a long stenosis involving the lower thoracic and upper abdominal aorta. A successful by-pass was secured by resecting the spleen, freeing the splenic artery distally and anastomosing the distal end of the splenic artery to the side of the lower thoracic aorta just proximal to the lower end of the constricted area.

The second type of coarctation which occurs below the region of the ductus arteriosus usually is found in the abdominal portion of the aorta slightly above, at or just below the level of the renal arteries. This stenosis is always localized and is believed to be congenital in origin. Maycock [14] suggested that this condition might be due to changes involving unequal fusion of the two dorsal aortas with obliteration and loss of one of them. The present case is the eighth reported case of coarctation of the abdominal aorta. The previous cases of this defect were reported by Maycock,[14] Steele,[15] Wang,[16] Bahnson,[8] Kondo,[17] Goldziehr [18] and Fisher.[19] In his review of the medical literature of this condition, Bahnson [8] included the case reports of Baylin [20] and Power.[21] However, Glenn [12] and others felt that these latter cases more probably represented examples of obliterating thrombosis of the aorta similar to that described by Leriche.[22]

In 1949 Wright [2] reviewed the literature of the "adult type" of coarctation of the aorta from the standpoint of determining the association of this condition with a ruptured cerebral artery aneurysm. This review included the 200 autopsied cases collected by Abbott [23] from the time of the earliest reported case in 1791 to 1928, and the 104 further cases collected by Reifenstein [1] from the latter date to 1947. In this group of 304 cases of "adult type" coarctation,

Wright [2] discovered 10 cases in which death was due to rupture of a clearly defined cerebral artery aneurysm. To this number he added an original case report of a healthy 19 year old girl admitted with an acute subarachnoid hemorrhage who was found at autopsy to have a ruptured cerebral aneurysm associated with a coarctation of the aorta. In this group of 11 cases the average age at death was 23 years; the youngest patient was 13 and the oldest 40. In addition, his review uncovered a case of a leaking aneurysm and four cases of unruptured aneurysms, making a total of 16 cases of coarctation of the "adult type" associated with cerebral artery aneurysm (5.2%) in which the diagnosis was confirmed at autopsy.

Bigelow [24] has recently reported the case of a 21 year old man with a known history of a coarctation of the aorta since the age of 13 who was admitted because of severe headache, convulsions and stupor. A ruptured intracranial aneurysm was suspected but could not be demonstrated by angiograms. Following his recovery from the cerebral symptoms a thoracotomy was performed and the coarctation was successfully repaired. However, one month later sudden death occurred and necropsy revealed a ruptured cerebral artery aneurysm.

Review of the 10 cases of coarctation of the lower thoracic aorta and the seven cases of coarctation of the abdominal aorta previously reported reveals that in none of these was there the finding of a ruptured cerebral artery aneurysm. However, in the case reported by Fisher [19] in 1952, two unruptured cerebral artery aneurysms were described as an incidental autopsy finding. This case concerned a 14 year old boy with malignant hypertension due to stenosis of the aortic orifices of the main renal arteries. The patient died postoperatively following a right nephrectomy. Necropsy revealed a coarctation of the abdominal aorta from immediately above the origin of the superior mesenteric arteries to a level beneath the origin of the renal arteries, with secondary severe stenosis of the renal, superior mesenteric and celiac arteries; an intracerebral hemorrhage of the left basal ganglia; a fusiform aneurysm of the lenticulostriate artery, and a berry aneurysm at the junction of the left cerebral and anterior communicating arteries. It would appear that the finding of these associated congenital vascular anomalies in this case and in our own case would provide further evidence that coarctation of the abdominal aorta is a congenital lesion. It is of interest in this connection also that the case reported by Kondo [17] revealed at autopsy a coarctation of the abdominal aorta and hypoplasia of both subclavian arteries, with an anomalous origin of the right subclavian artery from the aorta.

The association of hypertension with the usual "adult type" of coarctation of the aorta is well recognized and is attributed by some to ischemia [25] or other vascular disturbance of the kidneys. It is of interest that in our patient there was no known past history of hypertension and no autopsy evidence of left ventricular hypertrophy, and it may well be that the high blood pressure he exhibited terminally was entirely sequential to the intracranial hemorrhage. The finding of normal tension in a patient with a coarctation of the aorta below the renal arteries would be further evidence for the belief that arterial hypertension associated with coarctation above the renal arteries is renal in origin. However, it should be stated that in two of the previous cases of coarctation of

the abdominal aorta [8, 14] the area of the coarctation was entirely below the level of the renal arteries, and both of these patients had hypertension.

Summary

We have presented the case of a 77 year old man who died of a ruptured cerebral artery aneurysm and at autopsy was found to have a coarctation of the abdominal aorta. This is the eighth reported case of coarctation of the abdominal aorta and the first case in which rupture of an aneurysm of a cerebral artery occurred. The various types and locations of aortic coarctations are discussed briefly.

Acknowledgment

Grateful acknowledgment is made to Dr. David A. Rytand for his help in reviewing this article.

Summario in Interlingua

Coarctation del aorta abdominal es extrememente rar. Le presente reporto es le secunde de un caso con occurrentia simultanee de coarctation del aorta abdominal e aneurysma de un arteria cerebral e le prime de un caso in que le morte resultava del ruptura del aneurysma cerebral.

Le patiente esseva un masculo de 77 annos de etate qui habeva suffrite un accidente cerebrovascular. Un arteriogramma revelava un aneurysma saccular del arteria cerebral sinistro-anterior. Studios a injectiones aeree demonstrava un extense hemorrhagia intraventricular con formation de coagulo. Le patiente moriva e le autopsia confirmava que le ruptura del aneurysma habeva causate le hemorrhagia. Esseva etiam constatate un localisate coarctation del aorta abdominal comenciante a un puncto immediatemente infra le nivello del arterias renal e continuante un distantia de 4 cm usque al arteria mesenteric inferior.

Coarctationes del aorta es classificate le melio secundo le sitos de lor occurrentia. Un prime typo es le si-appellate "typo infantil" in que le restringimento es diffuse in le arco del aorta e occurre usualmente inter le arteria subclavicular sinistre e le ducto arteriose. Le secunde typo es le si-appellate "typo adulte" in que le coarctation es localisate al sito del ducto arteriose o immediatemente supra illo. Iste duo typos representa le grandissime majoritate del casos de coarctation del aorta.

Le tertie typo include le casos in que le coarctation occurre a o supra le nivello del diaphragma. Il existe 10 reportos de casos de iste typo de coarctation. In illos il ha invariabilemente un diffuse e elongate restringimento con evidentia de fibrosis periaortic lo que tende a supportar le conception que le condition es acquirite.

Le quarte typo de coarctation es incontrate in le portion abdominal del aorta, levemente supra o infra o al nivello del arterias renal. Le stenosis in iste casos es semper localisate e es considerate como congenite in origine. On ha opinate que iste condition poterea resultar de cambiamentos involvente un fusion inequal del 2 aortas dorsal con obliteration e perdita de un inter illos. Le caso hic reportate es le octave de coarctation del aorta abdominal trovate in le litteratura.

In un revista de plus que 300 reportos publicate de casos del "typo adulte" de coarctation del aorta, il esseva constatate que 17 de ille casos habeva etiam autopticamente confirmate aneurysmas de un arteria cerebral. Le serie total del reportos include 10 casos de coarctation del aorta thoracic inferior e 7 de coarctation del aorta abdominal, sed nulle inter istos monstrava un rupturate aneurysma cerebral. Nonobstante, il es a notar que un del previemente publicate reportos describe, inter altere

constatationes incidentalmente facite al autopsia, le presentia de 2 non-rupturate aneurysmas in un arteria cerebral. Le constatation de un aneurysma de un arteria cerebral in un patiente con coarctation del aorta abdominal supporta in nostre opinion le theoria que le coarctation del aorta abdominal es de origine congenite.

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CONGENITAL ANEURYSM OF THE LEFT VENTRICLE: A CASE REPORT *

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THE causes of an abnormal protuberance, or bulging, of the left ventricular contour, as seen on the conventional chest film, include ventricular aneurysm,[1] a localized syphilitic involvement of the myocardium,[2, 3] or a tumor of the heart or pericardium.[4] Other less likely causes are: an abscess or localized ulcerative lesion of bacterial endocarditis, loculated pericardial effusion, tuberculoma, and rheumatic involvement of the myocardium. Of these possible causes, ventricular aneurysm secondary to myocardial infarction is by far the most common, since approximately 8 to 10% of infarctions result in aneurysm formation.[1] It is probable that a careful search of the cardiac contour under the fluoroscope would result in the detection of more such cases. The other causes of aneurysm formation are quite uncommon and only a few scattered reports of each can be found in the literature.[8–15]

In the case to be presented there was an abnormal deviation or bulge of the left ventricular border as seen on a conventional chest film. The patient was observed for 14 years, during which time the cardiac contour showed no significant change. Autopsy revealed a ventricular aneurysm, the structure of which suggested a congenital origin. There was no anatomic or microscopic evidence of syphilis, rheumatic heart disease, coronary arteriosclerosis or myocardial infarction, or tuberculosis of the heart. A search of the literature fails to reveal a report of a similar case.

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Case Report

A 52 year old Negro male was first seen in 1931, at the age of 31, because of complaints of abdominal discomfort, indigestion and "fluttering" of the heart. Physical examination revealed no abnormality of the heart or cardiovascular system. Following the first visit the patient was thought to have a duodenal ulcer. He was placed on an ulcer regimen, following which all abdominal pain disappeared. Urinalysis revealed a trace of albumin and occasional hyaline and granular casts. During a series of ensuing visits to the Out Patient Clinic between 1931 and 1934 the blood pressure varied between 110/80 and 140/98 mm. of Hg. A chest film in 1934 showed thickening of the pleura bilaterally, but there was no mention of an abnormality of the heart contour.

In October, 1938, the patient was admitted to the hospital after an epileptiform attack. During the course of the investigation of this attack a routine chest film was reported to show an abnormal bulge of the upper left ventricular contour and

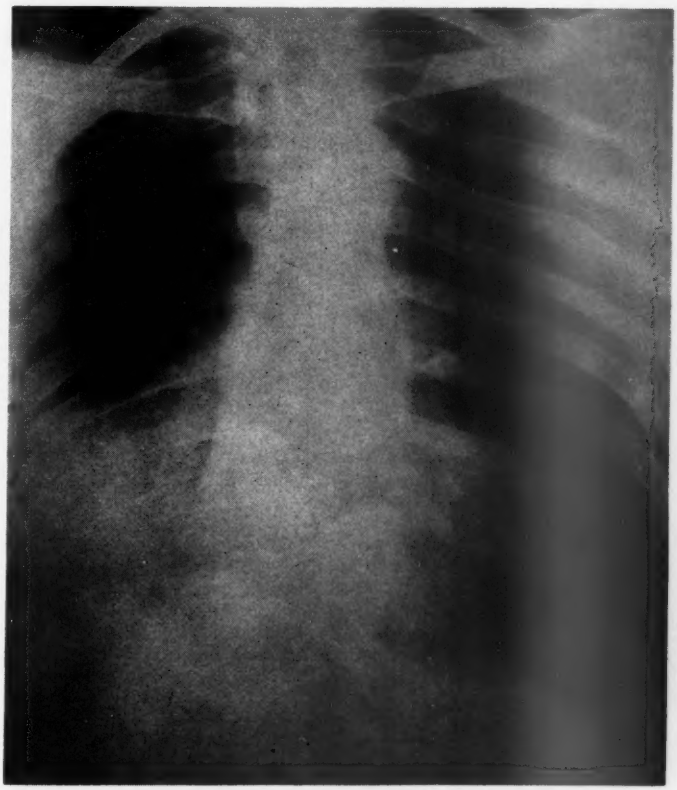

Fig. 1. *A.* Roentgenogram of chest showing the localized bulge along the left ventricular border, and increased density with scattered areas of calcification at the right base.

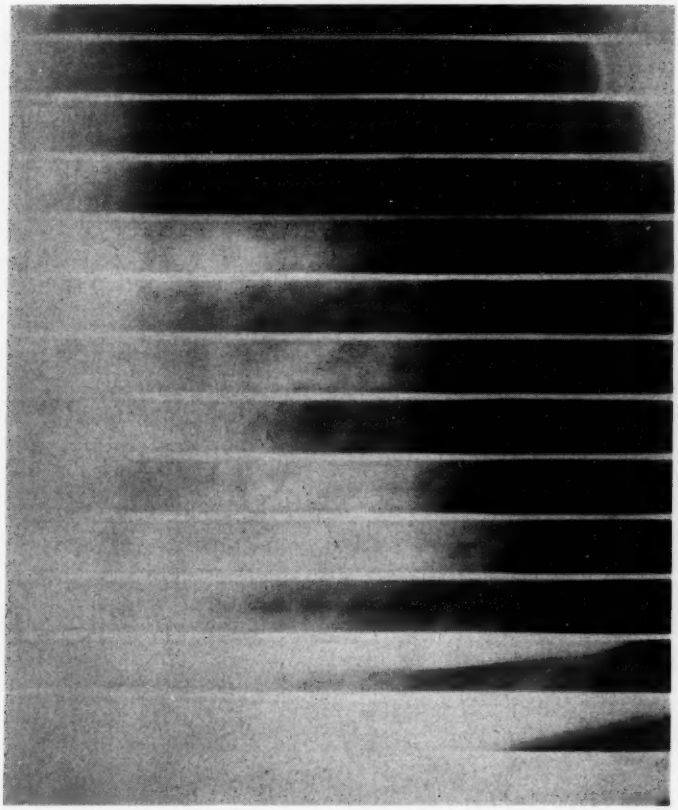

FIG. 1. *B.* Roentgenkymogram of left ventricular border revealing abnormal pulsations in the region of the aneurysm.

diffuse pleural thickening at the right base. Subsequent fluoroscopy showed expansion of this bulging contour during systole and contraction during diastole (paradoxical pulsation). Because of this a diagnosis of aneurysm of the anterolateral wall of the left ventricle was made. An electrocardiogram showed an inverted T wave in Lead I that was thought to be compatible with an anterior myocardial infarction. There was no evidence of heart failure and the blood pressure was within a normal range. There was no history of chest pain suggestive of myocardial infarction or coronary insufficiency.

During the next 14 years the patient returned to the Out Patient Clinic at irregular intervals. In 1939 he developed a uveitis which responded to desensitization with tuberculin.

In 1941 he had a severe convulsion which was followed by transient left-sided hemiplegia, but this cleared rapidly and no other significant change in his status was noted.

In 1944 the patient returned with an extensive skin rash and a positive serologic test for syphilis. He was given an extended course of antiluetic therapy, following which the serologic test for syphilis has been repeatedly negative.

During the period from 1938 to 1952 chest films on several occasions showed no significant change in the heart size or contour. The highest recorded blood pressure during this period was 160/100 mm. of Hg, and this was observed following an epileptic attack. The patient continued to have albuminuria with casts. The electrocardiogram continued to show abnormal T waves, but there was no other evidence of a cardiac abnormality. He continued to perform moderately heavy labor in a steel mill.

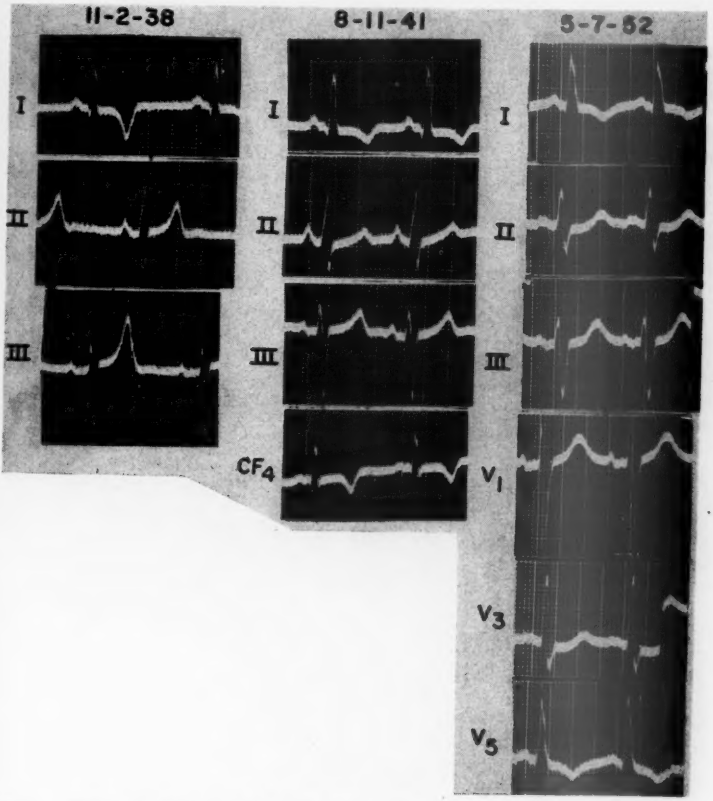

FIG. 2. The record taken 11–2–38 reveals a deeply inverted T_1.

The record of 8–11–41 reveals inverted T waves in Leads I and CF_4 although T_1 is not as deeply inverted as in the preceding record. T_3, while still positive, has decreased in amplitude.

The record of 5–7–52 reveals the pattern of left bundle branch block (QRS duration 0.12 second) with a prolonged QT interval (Q–T = 0.48 second, R–R = 0.76 second).

In January, 1952, the patient returned to the clinic because of dyspnea and weakness. The urine again showed red cells, white cells and albumin on repeated examinations. The nonprotein nitrogen was found to be 54 mg. %. The patient continued to do poorly and was admitted to the hospital.

On admission the blood pressure was 145/90 mm. of Hg and did not exceed 160/100 mm. of Hg during his hospital stay. Roentgen examination of the heart showed the bulging of the left upper contour and findings at the right base as previously noted (figure 1). Careful fluoroscopy and kymography showed definite diminished amplitude of pulsations of the lateral border of this bulge. However, the pulsations were not paradoxic, as had been reported in previous examinations; instead, they were in phase with the remainder of the left ventricular border. The heart was thought to be slightly enlarged. Calcification in the region of the right lung base was noted. An electrocardiogram revealed left bundle branch block (figure 2).

Kidney function was poor. A retrograde urogram showed an abnormality of the minor calyces of the left kidney, and it was thought that the patient had pyelonephritis. The nonprotein nitrogen continued to mount, and the patient developed gradually increasing and uncontrolled pulmonary edema, and died on the nineteenth hospital day. Repeated studies of sputa, gastric washings, bone marrow and urine for acid-fast organisms were negative, as were guinea pig inoculations.

Autopsy (performed by Dr. Donald Mark): There was a widespread granulomatous process with focal caseation and necroses in the hilar, para-aortic and axillary lymph nodes, lungs, spleen, liver and adrenals, but the heart was uninvolved.

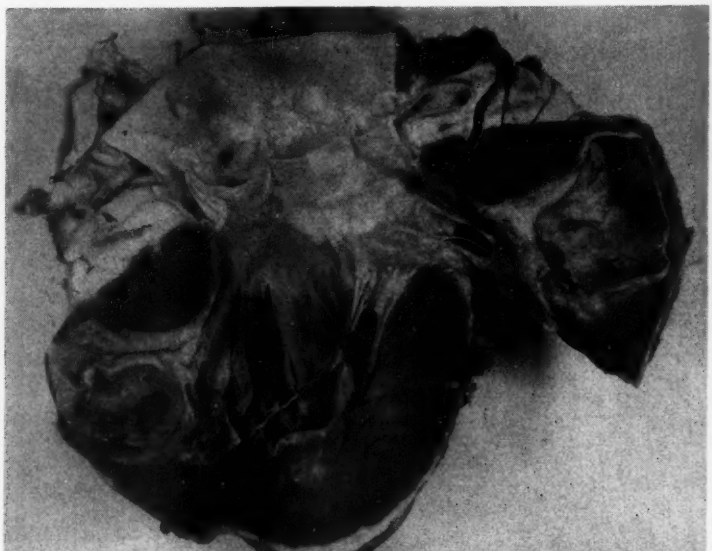

FIG. 3. Photograph of heart showing location and extent of ventricular aneurysm.

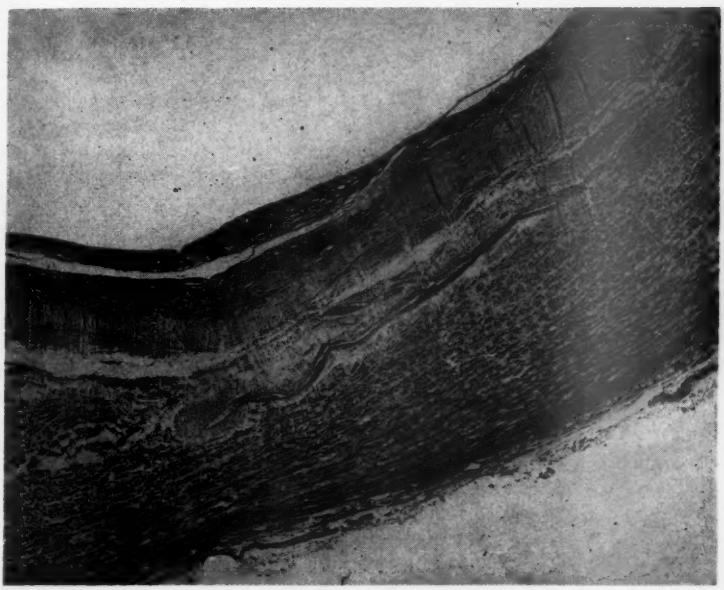

FIG. 4. Photomicrograph of wall of aneurysm showing thickened endocardium and atrophy of muscle (H & E × 20).

In addition, there was a partially calcified and caseous empyema of the right pleural cavity. Acid-fast stains of material obtained from mediastinal lymph nodes were not positive, but it is believed that the granulomatous process represented tuberculosis. Bilateral chronic pyelonephritis, hepar lobatum and focal ulcerations of the small and large intestine were also present.

The heart was enlarged and weighed 520 gm. The external surface was grossly deformed by a protuberance, or bulge, occupying the middle third of the left ventricular wall (figure 3). This bulge was due to a sac or aneurysm of the myocardial wall. The transverse diameter of the sac measured 3.5 cm. It was lined on its internal surface by a thick, yellow endocardial layer. The aneurysm communicated with the ventricular chamber by a small orifice measuring 0.5 cm. in diameter. The wall of the aneurysm was of variable thickness and measured 2 mm. at its thinnest point. There was no evidence of coronary arteriosclerosis, thrombosis or myocardial scarring. The right ventricular wall measured 5 mm. in thickness, and the left ventricular wall elsewhere was hypertrophied and measured 22 mm. in thickness. All valves were delicate and normal in appearance, and the chambers were otherwise within normal limits.

Microscopic examination of the heart revealed the wall of the aneurysm to be lined for the most part by hyalinized fibrous tissue, with some interlacing bundles of atrophic myocardial muscle fibers at the periphery (figure 4). Other sections were unrevealing, except for the presence of myocardial hypertrophy. The aorta was quite free of atherosclerosis.

Discussion

In this case there was no evidence of cardiovascular tuberculosis, syphilis, rheumatic heart disease, myocarditis or coronary artery obstruction. The aneurysm was lined by thickened endocardium and communicated directly with the cavity of the left ventricle. While it is believed that this represents an anomalous development of the left ventricle, no other anomalies, such as the presence of fetal intertrabecular spaces or endothelial lined channels [13, 15] in the aneurysm, were present.

It is probable that the associated left ventricular hypertrophy was a result of sustained hypertension; the exact role that this hypertrophy may have had in the development of the aneurysm is difficult to state. Whether actual aneurysm was present from birth or developed at a later date in response to functional demands on the heart is difficult to determine. Unfortunately, the original x-ray, which reportedly revealed no cardiac abnormality, is no longer available. However, from the time the aneurysm was first recognized (1938) until the time of death (1952) there were no significant changes in its radiographic appearance. Originally multiple fluoroscopic examinations revealed paradoxic pulsations; shortly before death the paradoxic pulsations were no longer demonstrable; instead, there was only a diminished amplitude of pulsations of this part of the cardiac border.

The initial electrocardiogram revealed decidedly abnormal T waves, and this was thought to support the diagnosis of aneurysm secondary to myocardial infarction. The later electrocardiographic changes, such as the presence of left bundle branch block, observed during the final admissions, were nonspecific. At no time were significant Q waves present. Although myocardial infarctions have been discovered at necropsy without definite evidence of coronary artery obstruction, this is infrequent and may be related to the thoroughness of the search for such a lesion. In this particular case a careful search failed to reveal any obstruction in the coronary arterial system; moreover, the coronary arteries were delicate throughout. In addition, the small opening (0.5 cm. diameter) to the aneurysm is unusual in aneurysms secondary to myocardial infarction. It seems improbable, therefore, that coronary arteriosclerosis was the cause of this aneurysm, although this possibility cannot be absolutely excluded.

While aneurysms of the heart were described not uncommonly during the 18th and 19th centuries,[5, 6] the cause was thought to be, for the most part, a fibrous myocarditis. In 1903 Hall [7] called attention to the role played by the coronary arteries in the etiology of such aneurysms. He stated: ". . . coronary endarteritis is the great cause of aneurysms of the left ventricle"—and mentioned the failure of many previous publications to describe the state of the coronary arteries. Since that time ventricular aneurysm, developing subsequent to myocardial infarction, has been recognized as a not uncommon complication.

Congenital aneurysm of the heart is much less common and may involve various structures: the sinuses of Valsalva,[7] the atrium,[8] interventricular septum [9, 10] and coronary arteries.[11]

Supposed or possible congenital aneurysms of the exterior wall of the left ventricle are, however, rare; few have been reported,[12, 13, 14, 15] and in the

majority of these the congenital origin is questionable. In all but one instance,[15] associated disease which might conceivably have been the cause of the aneurysm is mentioned as being present.

Marfie and Ingram[12] in 1920 described three cases of aneurysm of the left ventricle in native boys of the Gold Coast. One of these cases also revealed a gumma elsewhere in the heart, two of the three had an interstitial myocarditis, and all three revealed endarteritis of slight degree involving the coronary arteries. The authors believed that malaria may have been the cause of slight coronary endarteritis with subsequent aneurysm formation, although in retrospect the possibility of a congenital origin cannot be excluded.

Grant[13] in 1926 reported a case in which an aneurysm of the left ventricle was demonstrated in a 14 month old infant. The coronary vessels communicated directly with the aneurysm and many intertrabecular spaces were present in the myocardium. In addition, the heart showed a complicated anomaly with a single ventricle, patent ductus arteriosus, deformed tricuspid valve and pulmonary atresia.

Burn[14] reported a case of a 13 year old child with a saccular and loculated aneurysm of the lateral wall of the left ventricle which was believed to have originated from the fibrous tissue of the mitral ring. Aschoff bodies also were present in the myocardium.

Lovitt[15] recently observed a 62 year old white male who died of hypertensive cardiovascular disease who, at autopsy, revealed an aneurysm of the exterior wall of the left ventricle which was honeycombed in appearance and contained many endothelial-lined channels. The only other abnormality of the heart was left ventricular hypertrophy, and the aneurysm was thought to be congenital in origin. It seems that this is the only reported case which has good support for a congenital origin. It differs from ours only in the presence of endothelial-lined channels.

Other cases of aneurysms of the left ventricle have been reported in children. However, we have not reviewed cases without autopsy confirmation, or instances of aneurysm developing secondary to anomalous origin of the coronary arteries. The latter, in effect, are comparable to aneurysm secondary to infarction, or scarring of the myocardium due to inadequate coronary blood flow.

Summary

This is a case of aneurysm of the anterolateral surface of the left ventricular wall in a Negro male who died of chronic pyelonephritis with uremia. The aneurysm was first detected on a conventional chest film as an abnormal bulge of the left ventricular wall. The contour of the heart remained essentially unchanged during a period of 14 years prior to death. At necropsy the aneurysm appeared to be of congenital origin, and there was no evidence of coronary arteriosclerosis, myocardial infarction, rheumatic heart disease, syphilis or tuberculosis of the heart.

Acknowledgment

The authors wish to express their appreciation to Dr. William R. Milnor, Dr. Arnold R. Rich and Dr. Donald Mark for their assistance, criticisms and suggestions in the preparation of this report.

SUMMARIO IN INTERLINGUA

Nos discute brevemente le varie causas responsabile pro le presentia de anormal protuberantias del ventriculos sinistre in roentgenogrammas conventional del thorace. Nos presenta un caso de iste genere. Le patiente esseva un masculo negre de 52 annos de etate. Ille habeva un anormal protuberantia del ventriculo sinistre le qual esseva interpretate clinicamente como le manifestation de un aneurysma ventricular. Le patiente esseva observate durante 14 annos usque al tempore de su morte causate per chronic pyelonephritis con uremia. Al autopsia le plus significative tracto esseva un aneurysma del aspecto anterolateral del ventriculo sinistre. In vista del absentia de ulle clar factores etiologic e del presentia de certe characteristicas pathologic, il esseva considerate como probabile que le aneurysma esseva de origine congenite.

Nos presenta un breve revista del litteratura concernente le varie locos—atrio, septo interventricular, sinus de Valsalva, e arterias coronari—de aneurysmas cardiac congenite. Nos summarisa le pauco numerose casos incontrate in que tal aneurysmas involveva le ventriculo sinistre, e nos discute le datos supportante le conception que illos esseva de origine congenite.

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TOXIC REACTION TO MERCAPTOMERIN (THIOMERIN): CASE REPORT *

By Robert Lloyd Segal, M.D., *New York, N. Y.*

Of all diuretic drugs, the mercurial diuretics have the established advantage of combining effectiveness and safety when administered intramuscularly.[1] They may on occasion cause local or generalized reactions of varying degree. Chemical modifications of these organic mercurial compounds have been employed in an effort to minimize such toxic effects.[2, 3] Another mercurial compound, mercaptomerin sodium (Thiomerin) has recently been introduced. This preparation is an organic mercurial combined with a mercaptan (disodium salt of N-(gamma-carboxy-methyl-mercaptomercuri-beta-methoxy) propyl camphoramic acid). Formula: $C(CH_3)$, $C(COONa)(CH_3)$, CH_2, CH_2, $CH(ONH\ CH_2)CH(OCH_2)CH_2HgSCH_2$.

The stated clinical characteristics of mercaptomerin are:

1. It is an effective diuretic of low toxicity.
2. It may be administered subcutaneously as well as intramuscularly or intravenously.
3. It is equal or superior in potency to other mercurial diuretics.[4]

Mild local reactions to this drug have been reported, consisting essentially of clinically insignificant induration at the injection site.[5] There have been few reports of systemic or other reactions following the use of mercaptomerin.[4, 6, 7] It appears to be of interest and importance, therefore, to record the following example of such a phenomenon. In this instance, on initial injection and for a prolonged period, the administration of mercaptomerin invariably produced a thrombocytopenia, a prolonged clot retraction time and a fixed drug eruption.

Case Report

A 51 year old white male who had had attacks of rheumatic fever at the ages of 19 and 20 was being treated in the Cardiac Clinic of The Mount Sinai Hospital for chronic rheumatic heart disease (mitral stenosis and insufficiency, aortic stenosis and insufficiency), auricular fibrillation, and congestive heart failure. He had suffered a cerebrovascular accident seven years before, due presumably to an embolus. There were no known allergies or any other relevant past history.

In October, 1949, an examination disclosed the following findings: The patient was well developed, well nourished and comfortable. The heart was enlarged to the left, with the point of apical impulse in the sixth intercostal space, 16 cm. from the midsternal line. Systolic and rumbling diastolic murmurs were audible at both the apex and base of the heart. A short systolic thrill was palpable at the apex. The rhythm was totally irregular, with a ventricular rate averaging 100 and a radial pulse rate of about 90. The systolic blood pressure was approximately 130 mm. Hg and the diastolic 90 mm. Hg. The lungs were clear. The liver edge was palpable at the costal margin, and there was minimal pretibial edema. Some athetoid movements in the left upper extremity were the sole residua of the cerebrovascular accident. Therapy consisted of a low sodium diet, a maintenance dose of 0.1 mg. of

* Received for publication July 3, 1954.

digitoxin daily, and periodic intramuscular injections of various mercurial diuretics (such as Mercudem, Mercuzanthin and Mercuhydrin).

On October 24, 1 c.c. of mercaptomerin (Thiomerin) was administered subcutaneously for the first time. Three hours later the patient developed a reaction characterized by abdominal cramps and vomiting. Large, discrete erythematous patches appeared on his arms, legs, back, penis and gluteal regions. During the next 10 days bullous lesions developed in some of these erythematous areas (figures 1 and 2).

A second subcutaneous injection of mercaptomerin was given 14 days later and hematologic studies were carried out. Blood counts disclosed a reduction in platelets* to 70,000 per cubic centimeter. It was further observed that during the 24 hours following injection a marked prolongation of the clot retraction time oc-

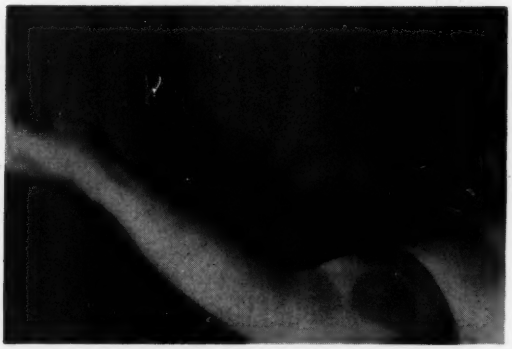

FIG. 1.

FIG. 2.

* All platelet counts were done by direct count in a standard counting chamber by the same technician with no knowledge of the clinical status of the patient. Counts were performed in duplicate and these agreed with each other within 10% or were repeated. The blood was drawn from a finger prick into a standard red blood cell pipet. Fresh 4% sodium citrate was used as a diluent. The normal platelet count according to this technic is 180,000 to 300,000 per cubic milliliter.

curred, concomitant with the fall in platelets. In view of this reaction to mercaptomerin the preparation was discontinued and other mercurials were employed. The platelet count returned to normal within three days, and after two weeks all the skin lesions had disappeared.

At this time, in order to test the constancy of this reaction to mercaptomerin, 0.1 c.c. of a 1 : 10 dilution of this drug was injected intradermally. Although no lesions appeared at the site of the injection, within 48 hours skin lesions appeared at the identical sites observed after initial administration of this diuretic.

On a third occasion, after a 30 day interval, following the subcutaneous injection of 0.6 c.c. of mercaptomerin, the manifestations already described were reproduced. Following every injection the patient developed nausea, abdominal cramps and some elevation in temperature. Skin lesions identical in pattern and morphologic detail appeared at the sites previously observed. Biopsy of one of the gluteal lesions showed "a skin fragment with minimal intra-epidermal edema and edema of the superficial dermis. No increased pigmentation."

It appeared evident from the foregoing observations that this patient reacted to the subcutaneous administration of mercaptomerin with a thrombocytopenia and a prolongation of clot retraction time, and with skin lesions of the fixed drug eruption type (table 1). Studies were then conducted to determine the effect on the patient's blood of other diuretics, principally Mercudem, Mercuzanthin and Mercuhydrin.

Table 2 lists an illustrative example of each of the foregoing mercurials and the associated hematologic and dermatologic response. It is clear that there was no change in the platelet count or in the clot retraction time, and that there were no associated skin lesions.

In addition to the foregoing, the Rumpel-Leede test was done and was found to be consistently negative. At the height of the manifestations of sensitivity to mercaptomerin, patch tests with the three mercurials mentioned above and mercaptomerin were performed, with negative results. The patient displayed no unusual reaction to a clinically effective dose of mercurous chloride (calomel).

Prothrombin determinations performed during the course of this investigation were always normal.

The electrocardiograms showed no change.

Discussion

Toxic symptoms and even death following the use of mercurial diuretics have been well documented.[3] These toxic manifestations can be grouped into three classes:

1. Symptoms related to and resulting from the associated diuresis.
2. Direct toxic effect of the mercury ion on specific organs.
3. Generalized manifestations of an idiosyncrasy or an allergic reaction to this group of drugs or specific members thereof.

The low salt syndrome—characterized by a confused mental state, dehydration, hemoconcentration and oliguria and, in severe instances, causing the clinical picture of shock—is well known. It is apparent that this toxic manifestation is nonspecific, and that it can be produced by any mercurial diuretic and could conceivably be produced by a nonmercurial diuretic.

Symptoms due to the toxic effect of the mercury ion, although rare, have been observed. They consist essentially of excessive salivation, stomatitis and hemorrhagic colitis.[3] Renal lesions consisting chiefly of the degeneration of the proximal tubular epithelium causing albuminuria and cylindruria, as well as

TABLE 1

Observations with Mercaptomerin

Time	Dose	Platelet Count	Clot Retraction	Rumpel-Leede	Skin Lesions	Blood Count
0	0.6 c.c. subcutaneously	220,000	—	—	0	
2 hrs.	—	—	—	—	3+	
48 hrs.	—	80,000	—	—	4+	WBC 8,800 Segs. 57 Non-segs. 3 Lymph. 34 Mono. 2 Eos. 4
4 days	—	100,000	—	—	4+	WBC 8,350 Segs. 64 Non-segs. 12 Lymph. 18 Mono. 4 Eos. 2
2 wks.	—	180,000	—	—	2+	WBC 8,100 Hgb. 14 gm. RBC 4.5 M Segs. 58 Non-segs. 6 Lymphs. 29 Mono. 2 Eos. 5
16 days	—	220,000	Normal	Neg.	2+	
		200,000	Normal	Neg.	2+	
		180,000	Normal	Neg.	2+	WBC 7,250
3 weeks		180,000			2+	Segs. 55 Non-segs. 4 Lymph. 33 Mono. 4 Eos. 4
0	0.6 c.c. subcutaneously	170,000	Normal	Neg.	0	WBC 7,800 Segs. 60 Non-segs. 6 Lymph. 29 Mono. 2 Eos. 3
24 hrs.	—	90,000	24 hrs.	Neg.	3+	
48 hrs.	—	75,000	—	Neg.	4+	
4 hrs.	—	200,000	Normal	Neg.	3+	
1 week	—	210,000	Normal	Neg.	2+	

microscopic hematuria and pyuria, have likewise been reported. It is interesting to note that in patients who have died suddenly after the administration of a mercurial diuretic, preëxisting renal disease is a frequent finding. The incidence of the foregoing toxic effects is astonishingly low when one considers the wide and frequent use of these organic mercurials. In the third category, i.e., symptoms ascribed to an idiosyncrasy or to an allergic response to this group of drugs, are included such reactions as chills, fever, cutaneous eruption and leukopenia.[8] The cutaneous eruptions are variable and include urticaria and morbilliform or scarlatiniform erythemas. The route of administration appears to be immaterial, and the dermatologic manifestations may occur with the initial or later injections. A cutaneous eruption may presage a more serious reaction.[10]

Fixed drug eruptions such as were observed in this patient have been reported after the administration of mercury salts and mercurial diuretics. These fixed drug eruptions are cutaneous manifestations which recur at the site of previously affected areas of the skin following the use of a specific drug. They

TABLE 2

Observations with Other Mercurials

Time	Platelet Count	Clot Retraction	Rumpel-Leede	Skin Lesions	Blood Count
2 c.c. Mercudem Intramuscularly					
0	200,000	Normal	Negative	0	WBC 7,000 Segs. 57 Non-segs. 3 Eos. 2 Mono. 3 Lymphs. 35
2 hrs.	230,000	Normal	Negative	0	
24 hrs.	190,000	Normal	Negative	0	WBC 6,900 Segs. 58 Non-segs. 3 Lymphs. 37 Eos. 2
2 days	210,000	Normal	Negative	0	
4 days	200,000	Normal	Negative	0	WBC 7,000
2 c.c. Mercuhydrin Intramuscularly					
0	200,000	Normal	Negative	0	WBC 7,000 Segs. 58 Non-segs. 4 Lymphs. 31 Eos. 3 Mono. 4
3 hrs.	240,000	Normal	Negative	0	
24 hrs.	200,000	Normal	Negative	0	WBC 8,100 Segs. 60 Non-segs. 2 Lymphs. 34 Mono. 2 Eos. 2
48 hrs.	210,000	Normal	Negative	0	
72 hrs.	180,000	Normal	Negative	0	WBC 7,300
2 c.c. Mercuzanthin Intramuscularly					
0	170,000	Normal	Negative	0	WBC 7,300 Segs. 55 Non-segs. 4 Lymphs. 33 Eos. 3 Mono. 5
2 hrs.	190,000	Normal	Negative	0	
24 hrs.	210,000	Normal	Negative	0	WBC 8,100 Segs. 64 Non-segs. 5 Lymphs. 25 Mono. 4 Eos. 2
48 hrs.	220,000	Normal	Negative	0	

may be erythematous or bullous in character, and may involve mucous membranes.[11] Desensitization may develop spontaneously or be produced artificially, with consequent alteration in the characteristic reaction to a specific offending medication.[2, 12, 13]

In the patient under discussion, such a fixed drug eruption invariably appeared after the administration of mercaptomerin but did not appear when any of several other mercurial diuretics were given, even when these were administered at the height of his reaction to mercaptomerin. It is interesting to note that when this patient was retested with mercaptomerin four years later there were no demonstrable skin lesions, thereby illustrating the spontaneous loss of sensitivity to which reference has already been made.

Unique in this case was the hematologic response, which consisted of a marked drop in the total platelet count and a prolonged clot retraction time. These effects were noted invariably, and persisted for 24 to 96 hours (table 1). Platelet counts did not deviate from the normal after the administration of other mercurial diuretics (table 2). There was no discernible effect on any of the other formed elements of the blood. Biopsy of the skin previously noted disclosed no platelet thrombi or agglutination. Such hematologic changes following the administration of mercurial diuretics have not been previously reported.[14] Snell and Rowntree reported, in patients with cirrhosis of the liver, four cases of purpura following the use of intravenous Merbaphen.[15] From the data in their paper there appears to be no constant or consistent change in the platelet count in the two cases in which such studies were carried out. It seems probable that the purpura was unrelated to the thrombocytopenia in these cases.

The mechanism of the described phenomenon is unknown.[12] In view of the absence of these effects when mercurials other than mercaptomerin were used, it appears to be a safe assumption that our patient was not sensitive to the mercury ion itself. The described toxic reaction(s) has never been observed in any other patient of the many who have received mercaptomerin in our clinic. In view of the extreme rarity of this complication, it is sufficient to record its occurrence. Mercurial diuretics have widespread application and frequent use. This isolated instance emphasizes their safety and, furthermore, indicates that untoward reaction to any one of the series justifies the trial substitution of another mercurial diuretic.

Summary

A hitherto unreported reaction to mercaptomerin (Thiomerin), characterized by thrombocytopenia, a prolongation of clot retraction time and a fixed drug eruption, has been described. This appears to be the first reported instance of such a phenomenon.

The administration of other mercurials did not produce these effects.

Acknowledgment

The author wishes to acknowledge with deep gratitude the generous help given by Dr. Samuel Averbuck, physician-in-charge of the Adult Cardiac Clinic.

SUMMARIO IN INTERLINGUA

Il existe in le litteratura reportos de leve reactiones local a mercaptomerina a natrium (Thiomerina®) sed paucos de reactiones generalisate o systemic. Le caso hic reportate es characterisate per le facto que initialmente e durante un prolongate periodo de tempore le administration de mercaptomerina resultava invariabilemente in thrombocytopenia, prolongation del tempore de retraction del coagulo, e fixate eruptiones medicamentose.

Le patiente esseva un masculo blanc de 51 annos de etate con chronic morbo cardiac rheumatic, stenosis e insufficientia mitral e aortic, fibrillation auricular, e chronic dysfunctionamento cardiac congestive. Le therapia consisteva in le prescription de un dieta a basse contento de natrium, dosages de mantenentia de digitoxina, e injectiones periodic de diureticos mercurial. Tres horas post le prime injection subcutanee de mercaptomerina le patiente reageva per crampos abdominal e vomito. Grande e discrete maculas erythematose appareva al bracios, gambas, dorso, penis, e in le regiones gluteal. In le curso del sequente 10 dies, lesiones bullose se disveloppava in alicunes de iste areas erythematose.

Post le secunde injection, studios hematologic esseva interprendite. Illos revelava un marcate reduction del conto del plachettas e un simultanee prolongation del tempore de retraction del coagulo. Intra tres dies le conto del plachettas retornava a nivellos normal. Le lesiones del pelle dispareva post duo septimanas. Omne iste phenomenos esseva reproducite per subsequente injectiones del mesme droga. Altere diureticos mercurial non induceva le mesme reactiones.

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EDITORIAL

STATISTICS AND THE CLINICIAN

Introduction

The purpose of this note is to explain a few principles—nothing esoteric but precepts of plain *common sense*—which underlie modern statistics. If one understands these principles one will be able to make sense of the statistical studies that are increasingly common in the medical literature. What is more, one will be able to decide whether or not the author's conclusions are believable *even though* one may not be able to make heads or tails of the formulas, computations, tables, or graphs which accompany the article! Of course if a physician wants to *write* statistical papers—not just read them—he will have to come to grips with mathematics and arithmetic!

Let me explain why it is possible to make a reasonably good judgment of a study without technical knowledge of statistics. It boils down to this: the results of a study obviously depend on the quality of *information* or data which was obtained. Any statistical procedure is device for extracting information—it can't *add* information. If the basic data contain a lot of misinformation, then the statistical methods extract this misinformation right along with the correct information. In other words if the data are badly biased then the conclusions from the data will reflect this bias. While, to a limited extent, statistical tinkering may partially compensate for the bias, the sad fact is that no amount of statistical manipulation can provide reliable results from seriously defective data.

Of course it is possible to start from sound data and make a mess of things by incorrect statistical analysis. This occasionally happens when the researcher does not really understand the methods he is trying to use. But this sort of error is much less serious. A competent statistician can spot this sort of mistake rather easily (however, defective data can—and sometimes do—fool an experienced statistician).

No, the real problem is to obtain sound data. There is, of course, no magic formula for success but during the past quarter century there has been developed a substantial body of design principles and technics. Most people are likely to think that a statistician should be called in at the end of a study to analyze the results—indeed 25 years ago this is what was done. Times change and the rôle of a statistician has changed. From my own experience as a statistical consultant, I would say that the time when my services are likely to be most useful to my colleagues is *before* the study has started. If a study is *well-planned,* if the *design* is appropriate, if the collection of the data is *well-controlled* then there is a good chance that the resulting information can be trusted. On the other hand, while hit-or-miss studies occasionally are fruitful, I would guess that more than 90% of these studies never lead anywhere (I would guess that less than half of such studies are even *completed*).

The Ingredients of a Study

To keep this discussion of design principles at a practical level it is best to consider these ideas in terms of a fairly specific experimental situation. The reader can test his understanding of these concepts by choosing a different type of study and then going through, step by step, to see how the notions apply in the chosen situation.

Let us consider a therapeutic trial. There are three basic ingredients in such a trial. First of all, there are the *individuals* under study—in the therapeutic example these might be a series of patients in a hospital clinic or service. The individuals considered here are assumed to have at least one thing in common: they are all diagnosed as suffering from some specified disease condition.

The therapy is supposed to achieve some goal—to cure the patient, to relieve pain or symptoms, or to prolong the patient's life. We must have some measure of success in achieving the specified objective and this measure I will call the *response variable*. The word "variable" means that the response may be different from one patient to the next. Sometimes we have several goals (for example, we may also want to avoid complications or side effects) and then we may have several response variables.

We may know (or suspect) that the response is affected by various factors. We are interested primarily in the effect of a particular therapy (which I will call "Drug A") but we realize that other factors may play a rôle. The severity of the disease, age or sex of the patient, previous medical history, etc. may affect prognosis. I will call these factors *stimulus variables*. We can further distinguish between *primary stimulus variables* (i.e. the ones we want to study) and *intervening stimulus variables* (i.e. the ones which may operate to obscure or confuse the results). What we would like to do is to *control* the *intervening stimulus variables* so as to obtain a clearer picture of the variables we wish to study.

There are two other important (but more easily overlooked) ingredients in a study. One of these is the person or team who carry out the study (and, of course, the resources available—personnel, time, and money). Although the "individuals" in a study are not always human the study itself is conducted by human beings. Since humans are known to be fallible, since they come equipped with opinions and prejudices, and since they must make essential decisions throughout the conduct of the study, they will necessarily influence the results of the study. Ideally the results should describe the phenomena under study and *not* the human beings who conducted the study. However, since the investigator is necessarily present, the closest that we can come to the ideal is to use procedures which *minimize* the influence of the investigator.

The fifth major ingredient is the *time-and-place* of the study. For the "exact" sciences, such as physics, the problem is much less acute than for the biological and medical sciences (indeed this is one of the main reasons why there *are* "exact" sciences). The physicist may set up his laboratory

almost anywhere on earth and still be able to reproduce the findings of his colleagues. Medical studies are far more sensitive to time-and-place effects. Results from two countries, or two states, or two institutions in the same city, or even two clinics in the same hospital may not be comparable.

These five ingredients must be carefully considered in planning, conducting, or judging a study.

Purposes of Design

The first principle of good design is to clearly formulate the *objectives* of a study. Therefore, in considering the question of good design we first need to form a definite idea of what we hope to achieve, in general, from a research study (much of the confusion about statistical methods arises at this point).

One objective is evident: we want to tell what happened in the course of the study. For example, if the study involved a series of post-operative patients given a new analgesic, Drug A, the response variable (obtained by questioning the patient) might be "relief" or "no relief." We might therefore describe what happened in the study by the summary statement: "75% of the patients reported 'relief' with Drug A."

Some folks would feel that the researcher's duty is discharged when this (and similar) summary statements were made. Having reported the results it would be up to the reader to draw any conclusions. For reports of case histories this might be appropriate since the purpose of the report might be to allow the reader to "re-experience" the experience of the attending physician.

It seems to me that the summary statement by itself does *not* achieve the objectives of a research study. As I see it, the conclusions of a research study are necessarily *predictive* in nature. If they are to be of any use to the clinician they must tell him something about the patients that *he* is going to see. In other words, a research study is interested in any particular series of patients mainly for what can be learned about *future* patients. This shift in *point of view* is, I believe, the main stumbling block that clinicians encounter in understanding statistics.

Evidently it is going to be a lot more difficult to make statements that will apply to *future* patients than it is merely to describe what has already happened. In order to make predictive statements it is necessary to make *inferences* about a class of patients (i.e. "population") on the basis of information from a limited number of individuals (i.e. "sample"). Distasteful as this chore may be—there is obviously some risk of making *incorrect* statements—it is a chore that a scientist cannot shirk.

The point of view expressed here, that the conclusions or findings of a study ought to be *predictive,* might be called a "forward-looking" standpoint to distinguish it from the "backward-looking" position (i.e. description of what has happened). If a clinician thinks solely in "backward-looking" terms then most modern statistical methods are essentially incomprehensible and meaningless.

Some Practical Points

Even if one is uninterested in scientific method or in medical theory (i.e. "academic" ideas) I still think it important to cultivate the "forward-looking" point of view purely for immediate practical reasons. Let us consider the summary statement, "75% of the patients given Drug A reported 'relief' " to see why it fails to meet the practical needs of the clinician.

First of all, the isolated statement provides no *basis for comparison.* Is this performance of Drug A good, bad, or indifferent? The only way to answer the question would be to have some kind of comparison figure for a familiar drug (say a standard dose of morphine) or perhaps for no drug at all (i.e. a placebo injection). In short the isolated summary statement is not really of much practical use as it stands.

Why can't we simply use some corresponding statement about morphine in the literature? The answer lies in the marked time-and-place effects already mentioned. The type of patients in the series, the method of conducting the trial, the measurement of patient response—these and many other factors blur the comparison of two numbers from different sources. Thus, for one thing, "relief" is necessarily a subjective quantity and various definitions are used ranging from "any relief" to "50% relief" to "complete relief." The number "75%" depends on what question is asked of the patient, how it is asked (and how often), who asks the question, and so on. Unless the comparison figure is obtained in a similar way to the original figure it is likely to be *biased* and may well be completely misleading. This, of course, is why good medical studies have "controls" or comparison groups in the *same* study.

For a statement like "this fish is 6 inches long" the comparison may be "automatic" because almost anyone's ruler will provide a reasonably good idea of the length "6 inches." But the measurements used in medicine (even such common ones as blood tests) do *not* have this sort of time-and-place stability.

Let us turn to another point. Suppose that we have two statements "75% of the patients report 'relief' from Drug A, 60% of the patients report relief from a standard dose of morphine." Should the clinician switch to Drug A? Surely he would first want to know how *reliable* these numbers are. The percentages give no indication—there might be a dozen patients in the series or several hundred. The practical meaning of the statements would be quite different in the two cases.

Put it another way: Could the researcher *reproduce* his results. If he did another series would it confirm his first series? This is one series (i.e. one sample); a second sample would be somewhat different (this ever-present phenomenon is called *sampling variation*). The difference in percentages in this particular series is 15% (75%–60%) but it would be extremely unlikely that, if we were to do a very large series of patients (so as to obtain a more reliable number) the figure would turn out to be *exactly* 15%. If we were to try to predict what would happen in the large series

and if we would hope to make a correct prediction we would have to predict an *interval* (example: "The resulting number would lie *between* 5% and 25%") rather than a single *point* (i.e. 15%). Nowadays such predictions are often found in medical papers. They are called *confidence intervals* because we have a reasonable degree of confidence that the prediction would be confirmed. The "degree of confidence" often used is the "5% level." This means that statistical methods have been chosen which (when properly employed) will lead to statements that will be wrong only about one time in twenty.

Although such confident interval statements may seem strange at first (why say "between 5% and 25%" when the difference in the actual series was 15%?) they have a distinctly practical value. Numerical differences in percentages are often quite misleading. There is no point in getting excited about differences which can readily be explained by everpresent sampling variation.

Perhaps this argument is still too abstract. Let us very briefly consider the actual consequences of the "looking forward" point of view. We see that "looking forward," thinking of conclusions as predictive rather than descriptive, forces us to consider such things as bases of comparison, control of biases, and sampling variation. It makes us look at how the particular series (sample) was obtained, how the study was conducted, and what range of application the conclusions can have. It leads us to ask all sorts of questions—questions which only are *meaningful* if we are "looking forward."

What happens when we don't ask these questions? Look at the painful record of the past. How many "wonder" therapies have been acclaimed on the basis of a haphazardly collected series of case histories (without adequate controls) only to be found, eventually, to possess no merit? How many genuine advances have been submerged in a flood of controversy (based largely on miscellaneous case histories) so that decades passed before their potential was realized?

Possibly I am overoptimistic but I believe that there has been a pronounced improvement in medical studies in the last 10 years. Would it have been possible in the twenties to make a mass vaccine trial which gave placebo injections to half of the children (and thus to get more information in a single year than could have been obtained in a generation of small uncontrolled studies)? Compare the careful bioassay designs used today with the haphazard assessments of biological preparations that once were made. Contrast the coöperative testing programs used to evaluate antibiotics nowadays (e.g. penicillin and syphilis) with the old procedures that represented little more than a clinician's opinion of some few cases. In many, but not all, areas of medicine the transition from hit-or-miss little studies to carefully planned research is currently taking place.

Designing a Study

Now let us consider from the "looking forward" point of view some of the principles of good design. It is not feasible to describe here, or even

list, the wide variety of design technics currently used in medical studies. The best that I can do is to give a little picture of how, in the previously considered analgesic trial, it is possible to use various devices to deal with some of the problems that arise in such a trial. If the critical reader looks for some mention of these and other design devices he can tell rather easily whether or not a given study has taken advantage of the modern design principles.

Q. How can we obtain a *basis for comparison?*

A. Ordinarily the best way is to include alternative therapies in the basic design. For example, we may include Drug B (a standard dose of morphine) and Drug C (a placebo injection of saline). To obtain a better picture of the relative efficacy of Drug A we might use at least *two* dosages of A (say x units and 2x units) and at least two doses of morphine (one dose double the other).

Q. How can we make a fair allocation of patients to the different therapies?

A. The key to a fair test is the use of *randomization.* Randomization is nothing more than the use of a chance mechanism (such as coins, dice, or better yet, "random number tables") to make the decisions. Since ancient times it has been intuitively evident that gambling devices can lead to a "fair" allocation. Thus our word "decimation" comes from the ancient practice of dealing with mutinous troops by executing one soldier in ten with the unfortunate soldier chosen by lot. Nowadays the use of randomization can be given a solid and rational basis as a result of many theoretical and experimental investigations.

Q. Suppose that only one drug can be tested on a given patient. How could a series of patients be assigned at random to different therapies?

A. The technic is very simple. Number the patients consecutively. Then use a random number table to draw the required sets of random numbers. The random number table can be replaced by other chance mechanisms. For example the numbers could be written on an ordinary deck of playing cards. After thorough shuffling the cards could be dealt into as many piles as there are therapies under test. There is one important point to note: a random sample is obtained in a carefully *prescribed* manner. In everyday usage the word "random" is sometimes used as a synonym for hit-or-miss or haphazard selection. However in statistics "random" and "haphazard" are not at all the same. For example, reaching into a cage of laboratory animals and picking the closest ones is not a *random* sample. It may happen that such haphazard sampling will select less active or larger animals and therefore be biased.

Q. Suppose some of the patients are known to suffer from very severe pain. Shouldn't such patients be given a drug whose effectiveness was known rather than possibly ineffective Drug A?

A. This sort of ethical problem often comes up in practice. It may well be that certain types of patients are not suitable for a given study or for some therapy in the study. The way to handle this is to set up, *in advance if possible,* criteria of suitability. These should be listed in the paper. The random principle requires that each patient should have the same chance (ab initio) of receiving the therapies under test and if this is impossible the patient should be excluded from the trial. Omitting a class of patients means, of course, that the trial will *not* give information about this class of patients. The test will still be a fair test but it will have a restricted *range of application.*

Q. Suppose the response is known to depend on certain patient characteristics such as sex, age, previous severity of pain, etc. Wouldn't it be better to balance the series than to allocate at random?

A. Balancing may give a much better comparison. However we can have our cake and eat it *too* in this instance. What we do is to divide the series into sub-series according to whatever patient characteristics we may believe to be important. We then assign patients at random *within* the sub-series. The nice thing about this procedure is that the assignment to category may depend on personal judgment but the test is still *fair* if the *final* assignment is random. If the factors are really important we may stand to gain but if it turns out that some or all of the factors are irrelevant we are not likely to lose very much. In general we may get more information about the therapy from each case and we also may obtain information about the factors (other than therapy) which influence the response.

Q. Can we assign patients at random when we do not know in advance how many patients will appear in a sub-series?

A. Yes, there is a simple device for this purpose.

Q. Suppose that a patient could receive more than one drug (allowing time intervals for the effects of each drug to disappear). Would we use the previous designs?

A. No, now there is a better plan because each patient would serve as his own control and we would expect the variation *within* a patient (i.e. in responses of the same patient at different times) to be less than the variation *between* patients. If at all possible we should want each patient to receive *all* the therapies under test. We would, however, want to randomize the *order* of the different treatments. For example, we would *not* want to give all patients the therapies in the same order.

Q. In the above situation time effects might enter. For example, during one period it might be very humid or unpleasant and this could affect patient response. What could be done to control the time factor?

A. There are a number of design devices to deal with this problem. One of these is to balance the study in *each* time interval. The *Latin Square* given below is one such method:

	Time Interval			
Patient	1	2	3	4
1	A	B	C	D
2	D	A	B	C
3	C	D	A	B
4	B	C	D	A

Thus patient 1 is given Drug A first, patient 2 is given Drug D first, etc. Note that in each time period all four drugs are given so that this plan is balanced over *time*. The above design would be randomized in actual use but the principle is clearer in the unrandomized form given above. This design came in very handy in a test of laxatives where a one-week time interval was used. It so happened that in the last week there was a mild epidemic of diarrhea among the patients. This was easy to spot since all the test laxatives were very "effective" that week. Had the patients all been receiving the *same* laxative at that time we would have probably missed the epidemic and given that laxative the credit!

Q. Suppose there are more time periods possible per patient than there are therapies under test. Could the whole study be repeated?

A. Yes, and wherever possible such repetition (technically: *replication*) should be used. It gives us a *direct* picture of the variation in a patient's response over time. The plan should be re-randomized in each repetition.

Q. Now what about psychological effects? Suppose a patient believes that he gets relief only from a particular drug. Might not his belief affect his response?

A. Yes, it may. So what we do is use a "blind" design. The different therapies under test are presented to the patient in the same form. This is fairly easy with injections and pills. Sometimes, in other studies, this takes considerable ingenuity (and sometimes it can't be done).

Q. But what about the nurses? Suppose they favor some therapy. Wouldn't this bias the response?

A. It might. But we can use a "double blind" design. The drugs are designated only by a code symbol and this code is known only to a third person. This same "blind" principle may be used in other types of studies. For example, in retrospective studies of smoking and lung cancer it may be possible to arrange things so that the person who interviews a patient does *not* know whether this patient will fall into the "lung cancer" or the "control" series.

Q. People always make mistakes. Clerical errors creep in. What can you do about such errors?

A. Some mistakes will, it's true, get into the final results. Most such mistakes can be caught beforehand by what is known as "quality control" of the clerical operations. These operations tend to be rather complex in modern studies but flow charts, editing, reëditing, spot checks, cross checks, and other devices can be used to control such errors.

Q. What about major errors such as wrong diagnoses, false responses, or misclassifications of a patient's characteristics?

A. Naturally such error may affect the results. However with a balanced and randomized design what ordinarily will happen is that the findings will really be *more* significant than the statistical procedures indicate.

Q. So far we have been talking mostly about a "fair" design which would control biases and artifacts. Even if the design is fair it is still subject to sampling variation. What about that?

A. True enough, sampling variation is present but, if the design is sound, it is relatively easy to control this factor. By and large modern statistics provide excellent *analytic* tools for dealing with sampling variation. We can readily determine whether sampling variation is likely to explain the results by using *significance tests.* We can make estimates of efficacy using *confidence intervals.* Thus the chances of being misled by sampling variation can be made quite small if the statements and conclusions are made on the basis of modern statistical methods.

The statements about risk of error should be interpreted in the following sense. If the study were repeated using, say, a very large series of patients from the same *population* sampled by the original study then the conclusions or statements would rarely be "reversed" by the new study. One point that the clinician ought always consider when he contemplates using the results of a study—he may be dealing with quite a different type of patients from those reported in a paper.

Q. Doesn't this mean that the clinician should always have some reservations about the conclusions reported—even in a well-designed study?

A. Yes, it is always a good idea to be cautious about the results of any single study. No one study done at a particular institution and at a given time can control time-and-place effects. That is one reason for the modern trend toward nationwide coöperative studies. For the same reason it is customary in all sciences for researchers to try to reproduce the results of previous studies, especially if the results are novel or important. Although no "absolutely certain" results are ever obtained in science, the chances are that if a number of independent studies lead to similar results then these results can be used in practice.

There is one point that deserves special emphasis insofar as time-and-place effects are concerned. In general *relationships* show much more stability than *incidences.* Thus the *relationship* between the efficacies of Drug A and Drug B (ex. "Drug A is more effective than Drug B") may be confirmed even though further studies may come out with quite different numerical estimates of the respective efficacies. This same effect shows up when different laboratories perform "blind" chemical analyses of a set of samples. The numerical estimates of a given sample often are considerably different from lab to lab. However, the *relationship* between two samples is likely to be fairly consistent from lab to lab. The reason for the stability of relationships is that the *biases* tend to cancel out.

IRWIN BROSS, PH.D.

REVIEWS

Foetal, Infant and Early Childhood Mortality. Vol. I: The Statistics. Vol. II: Biological, Social and Economic Factors. Volume I—137 pages; 28 × 21.5 cm. (paper-bound). Volume II—44 pages; 28 × 21.5 cm. (paper-bound). Department of Social Affairs, Population Division, United Nations, New York; available from International Documents Service, Columbia University Press, New York. Price, Volume I: $1.50; Volume II, 40 cents.

These two volumes present, as the titles indicate, accumulated data and interpretation in the field of mortality of young children. They were prepared by the Population Division of the United Nations Department of Social Affairs in compliance with a resolution of the Economic and Social Council directing the accumulation of data relating to mortality, especially infant mortality. They include a great mass of information collected from all continents and over 60 countries embodying birth rates, stillborn, neo-natal and infant death rates, correlations of mortality rates with income, illiteracy, nutritional levels, parity and other factors. In the first volume, edited by Dr. Joseph U. De Porte, there is analysis and interpretation of the volume and reliability of the statistics, the incidence and nature of abortions and stillbirths, the causes of infant mortality and briefly the conclusions reached from study of these statistics. It is striking that, in only 5 of 35 countries, where infant mortality rates were comparable on an international level, was the rate less than 50 deaths per 1000 live births. Thirteen countries reported rates of 50 to 100, ten from 100 to 200. In certain countries 20% of all live born children did not survive the first five years.

In the second volume, for which Dr. Louis I. Dublin was advisory editor, one section presents analyses of the causes of this tremendous wastage of reproduction in terms of such biologic factors as maternal age, birth order, frequency of birth, multiplicity of births and duration of pregnancy. The second major section surveys the mortality statistics from the point of view of such socio-economic factors as illegitimacy, nutrition of parent and infant, housing, social grouping, rural or urban residence and family income. The final conclusion, which this reviewer finds optimistic, is as follows: "The vicious circle which, according to some writers ties together excessive fertility and high mortality with poverty, can be broken by intelligent planning and the improved utilization of the material and human resources of each country."

The worldwide aspects of the information presented emphasize the tremendous strides made in a few socio-economically advanced areas over all of the remainder of this globe.

The data presented will be invaluable to researchers in the field of abortion and infant mortality and to a limited extent in general socio-economics.

RUSSELL S. FISHER, M.D.

Angina Pectoris. By Prof. Dr. W. H. HAUSS. 394 pages; 24.5 × 17.5 cm. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. 1954. Price, Ganzleinen DM 59.40.

Under the title of angina pectoris, the author discusses all known pathological states which produce chest pain of "anginal nature." The analytic approach, the description of the differential diagnosis, and that of the various causes giving rise to it, are done with conciseness and clarity. In spite of the broad scope chosen, the main emphasis is upon the chronic and acute forms of the degenerative diseases of the coronary circulation. Its anatomy and pathology are described in the conventional manner. The reviewer feels that although our knowledge of the physiology of the

coronary circulation and muscle metabolism, dynamic, biochemical and neural, are most limited, more space should be devoted to it in the next edition. The differentiation of myocardial necrosis and chest pain from coronary insufficiency and coronary occlusion is clearly analyzed. The clinical, laboratory and electrocardiographic changes are equally well described. In an attempt to give a "complete" survey of disease states leading to chest pain, the author includes at times more than is warranted even on the basis of the most extensive clinical experience: heart attacks in Libman-Sacks disease or acute disseminated lupus erythematosus if they occur at all, are too rare to be considered in differential diagnosis.

Therapy of coronary sclerosis with angina pectoris is discussed in the conventional manner with a discussion of all popular drugs. This is devoid of any critical evaluation and therefore of specific recommendations. Since few principles are really effective these few should be emphasized above the mass of useless or near to useless drugs.

Prolonged hypothermia as advocated by Laborit and Huguenard is described at length. Although the physiological basis for "hibernation" in acute myocardial infarction is logical, its recommendation must await critical study of factors and rationale involved.

These few criticisms are not meant to distract from the fact that Dr. Hauss' book is excellent, clearly and concisely written, a most valuable contribution. Printing and reproduction of illustrations are of superior quality.

A. G.

Multiple Sclerosis. By DOUGLAS MCALPINE, M.D., F.R.C.P., Physician-in-Charge of Department for Nervous Diseases, The Middlesex Hospital, London; NIGEL D. COMPSTON, M.A., M.D. (Cantab.), M.R.C.P., Assistant Physician, The Royal Free Hospital and Hampstead General Hospital, London; and CHARLES E. LUMSDEN, M.D. (Aberd.), Sir Henry Head Research Fellow of the Royal Society. 304 pages; 24.5 × 15.5 cm. The Williams & Wilkins Co., Baltimore. 1955. Price, $7.00.

This volume is based on the authors' experience in a study of 1,072 patients with multiple sclerosis. Smaller groups of this number were studied more extensively for specific purposes. Their experiences are presented in the light of work done by others so that there is included in this volume a review of most of the data available concerning multiple sclerosis. The material is presented under headings of symptomatology, etiology, laboratory findings, clinical course, differential diagnosis, treatment and pathology. There is, in addition, a section on the related demyelinating diseases in which not only those naturally occurring in man and animals are discussed but the experimental allergic encephalitides are also included. There is a short concluding section where problems of etiology are discussed and again all views are presented, as well as those held by the writers, specifically the rôle played by the oligodendroglia in myelination and demyelination.

The chapter on treatment departs somewhat from the general plan of presentation in that the views and results of the authors are presented as usual but those of others are incompletely discussed. It is also believed that methods of evaluating treatment are important enough to have justified a more complete discussion.

Each chapter is followed by a bibliography and the volume is concluded with both an index of authors and a subject index. The illustrations are chiefly concerned with pathology and are clear and informative. This volume constitutes a balanced and instructive discussion of the current status of multiple sclerosis. It is a valuable reference volume and would be useful in the library of any physician but particularly those interested in diseases of the nervous system.

C. V. B.

Reserpine in the Treatment of Neuropsychiatric, Neurological, and Related Clinical Problems. Editor: ROY WALDO MINER; Conference Co-Chairmen: FREDERICK F. YONKMAN, FRANK L. MOHR, and JOCK L. GRAEME; Consulting Editor: FREDERICK F. YONKMAN. 280 pages; 23 × 15.5 cm. (paper-bound). The New York Academy of Sciences, New York. (From the Annals of the New York Academy of Sciences, Volume 61, Art. 1, pages 1–280, April 15, 1955.) 1955. Price, $3.50.

This publication contains the series of papers presented at a conference held by the Section of Biology of the New York Academy of Sciences in February of 1955. It represents the most comprehensive single source of information on reserpine available to date. The subject matter ranges from experimental neuropharmacology to clinical dermatology, although the bulk of the 31 papers deal with the use of reserpine in clinical psychiatry. The absence of any firm theoretical footing in "psychopharmacology" makes such clinical and anecdotal papers essential to both clinician and investigator. For example, reserpine clearly has a powerful central "tranquilizing" effect. Unhappily, we must circularly redefine "tranquility" as the end result of taking reserpine, since this new "tranquility" ranges from euphoria to suicidal depression. Some day we will have more transactional generalizations, and our descriptions of drug actions will take into account the state of the organism being drugged. Until that day, we may point out the obscurity of another worker's therapeutic goals, and quibble with his criteria for cure, but we will have to continue relying on case reports and vague statistical summaries.

We should be further along if all such studies were up to the level set in this collection of papers.

ENOCH CALLAWAY III

A Compilation of Paintings on the Normal and Pathologic Anatomy of the Reproductive System. Volume 2 of The Ciba Collection of Medical Illustrations. Prepared by FRANK H. NETTER, M.D.; edited by ERNST OPPENHEIMER, M.D.; with a foreword by JOHN ROCK, M.D., Clinical Professor of Gynecology, Harvard Medical School. 302 pages; 32 × 24 cm. Commissioned and published by Ciba Pharmaceutical Products, Inc., Summit, N. J. 1954. Price, $13.00 (sold at cost).

This volume very fully covers the embryological development and the anatomy of the genital tract of both sexes. The pathological conditions of both male and female are logically presented. Space is allocated to Dr. Netter's excellent drawings and to a very concisely and adequately portrayed written description of the problem under discussion. The drawings are very accurate, colorful, and give an impression of third dimension which makes the interpretation and understanding of the drawing simpler.

More time might be devoted to the more common lesions; for example, carcinoma of the cervix and uterus, and a less complete description of some of the rare pathological entities.

This volume serves a worthwhile purpose for the specialist and general practitioner and should be available to medical students so that they may profit by the audiovisual presentation of those conditions affecting the generative tract of the male and female.

W. K. D.

Pathology. By PETER A. HERBUT, M.D., Professor of Pathology, Jefferson Medical College; and Director of Clinical Laboratories, Jefferson Medical College Hospital, Philadelphia. 1227 pages; 26.5 × 18 cm. Lea and Febiger, Philadelphia 6, Pa. 1955. Price, $16.00.

Designed as a student text, this book presents as one of its outstanding merits, the orderly arrangement of a voluminous amount of factual information compiled with "little if any adornment." This arrangement, while distinctly advantageous, in a few instances precludes proper emphasis being given to anatomical lesions of importance in the clinical manifestations and course of a given disease process. Similarly, references to pathologic physiology are not elaborate.

Chapters on the evolution of pathology and the procedure and purposes of autopsy precede chapters which treat of the general aspects of congenital anomalies, degenerations, inflammation, physical disturbances and tumors. This pattern is then followed in presenting discussions of the various organs and systems. The individual topic is described in terms of definition, incidence, cause, gross and microscopic appearance, complications, clinical manifestations, treatment and prognosis with emphasis, of course, on morbid anatomy.

Illustrations are numerous, of adequate size and have obviously been chosen with considerable care.

R. B. T.

Diagnostic Advances in Gastrointestinal Roentgenology: Selected Methods, with Clinical Evaluation. By ARTHUR J. BENDICK, M.D., Director of Radiology, Beth Israel Hospital, New York. 131 pages; 26 × 17.5 cm. Grune & Stratton, Inc., New York. 1954. Price, $6.00.

This book is not a comprehensive treatise on gastrointestinal roentgenology but a brief one summarizing only the recent technical and diagnostic developments. The author reviews controversial points in detail and briefly discusses newer diagnostic points, often concluding with his own personal opinions. The newer apparatus and technics which have improved and often simplified gastrointestinal roentgenology are discussed.

The book is easily readable and well illustrated with numerous excellent radiographs. However, the book is not intended for beginners but for radiologists and gastro-enterologists.

J. M. D.

BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Anxiety and Stress: An Interdisciplinary Study of a Life Situation. By HAROLD BASOWITZ, HAROLD PERSKY, SHELDON J. KORCHIN and ROY R. GRINKER, from the Institute for Psychosomatic and Psychiatric Research and Training of the Michael Reese Hospital, Chicago. 320 pages; 23.5 × 15.5 cm. 1955. The Blakiston Division, McGraw-Hill Book Company, Inc., New York. Price, $8.00.

The Biologic Effects of Tobacco, With Emphasis on the Clinical and Experimental Aspects. Edited by ERNEST L. WYNDER, M.D., Head, Section of Epidemiology, and Associate, Sloan-Kettering Institute for Cancer Research; foreword by JOSEPH GARLAND, M.D., Editor, *The New England Journal of Medicine.* 215 pages; 21 × 14 cm. 1955. Little, Brown and Company, Boston. Price, $4.50.

Cardiology Notebook for Preliminary Instruction in Medical Curricula, Columbia University College of Physicians and Surgeons. Editorial Board: ALFRED P. FISHMAN, M.D., Chairman; M. IRENÉ FERRER, M.D., RÉJANE M. HARVEY, M.D., JOHN H. LARAGH, M.D., DICKINSON W. RICHARDS, M.D., and JOSEPHINE S. WELLS, M.D. 97 pages; 26 × 20 cm. 1955. Grune & Stratton, Inc., New York. Price, $2.50.

Ensayo de una Teoria Unificada de la Medicina, Patología de la Totalidad: Coleccion de Monografias Suplementos de Folia Clinica Internacional. Edited by F. ARASA. 183 pages; 23 × 16 cm. 1955. Folia Clinica Internacional, Barcelona.

Die Funktionelle Beurteilung des Lungen- und Herzkranken. By DR. MED. HERIBERT C. LANDEN. 166 pages; 22.5 × 15.5 cm. (paper-bound). 1955. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, brosch. DM 22,-; geb. DM 24,-.

Die Geschichte der Organisation der Kreislaufforschung in Deutschland. By Prof. DR. MED. BRUNO KISCH, New York. 22 pages; 24.5 × 17 cm. (paper-bound). 1955. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price; kart. DM 2,-.

The Human Adrenal Cortex: Ciba Foundation Colloquia on Endocrinology. Volume VIII. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and MARGARET P. CAMERON, M.A., A.B.L.S.; assisted by JOAN ETHERINGTON. 665 pages; 21 × 14 cm. 1955. Little, Brown and Company, Boston. Price, $10.00.

Influence de certaines industrialisation outrancières sur la santé et particulièrement sur la progression continue de la morbidité cancéreuse: prophylaxie du cancer. By R. REDING. 50 pages; 24.5 × 16 cm. (paper-bound). 1955. Imprimerie Medicale et Scientifique (S. A.), Brussels. Price, 50 cents.

Investigations on Genetic Aspects of Carcinoma of the Stomach and Breast. By CHARLES M. WOOLF. 85 pages; 23.5 × 15.5 cm. (paper-bound). 1955. University of California Press, Berkeley. Price, $1.00.

Ionography: Electrophoresis in Stabilized Media. By HUGH J. MCDONALD, D.Sc., Professor of Biochemistry, Stritch School of Medicine of Loyola University, Chicago; in collaboration with ROBERT J. LAPPE, M.S., Research Assistant, Department of Biochemistry, Loyola University; EDWARD P. MARBACH, Ph.D., Associate Chemist, American Meat Institute Foundation and Research Associate (Instructor), Department of Biochemistry, University of Chicago; ROBERT H. SPITZER, M.S., Research Assistant, Department of Biochemistry, Loyola University; and MATTHEW C. URBIN, Ph.D., Associate Chemist, Chemical Division, Corn Products Refining Company, Argo, Illinois. 268 pages; 22.5 × 14.5 cm. 1955. The Year Book Publishers, Inc., Chicago. Price, $6.50.

Leistung, Ermüdung, Sicherheit. Band 3. Verhandlungen der Deutschen Gesellschaft für Arbeitsschutz. By DR. MED. E. MAGER, DR. MED. P. ROSENBERGER and DIPL.-ING. H. STEEG. 282 pages; 23 × 15.5 cm. (paper-bound). 1955. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, kart. DM 25,-

Malaria: A World Problem. By E. J. PAMPANA, M.D., Chief, Malaria Section, World Health Organization; and P. F. RUSSELL, M.D., M.P.H., Division of Medicine and Public Health, Rockefeller Foundation, New York, N. Y., etc. 72 pages; 24 × 18 cm. (paper-bound). 1955. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 70¢.

Management of Disorders of the Autonomic Nervous System. By LOUIS T. PALUMBO, M.D., Chief, Surgical Service, Veterans Administration Hospital, Des Moines, etc. 186 pages; 21 × 14.5 cm. 1955. The Year Book Publishers, Inc., Chicago. Price, $5.00.

La Medicina Norteamericana Actual a Través del Médico Español. By FRANCISCO BARNOSELL, FRANCISCO CANIVELL, ANTONIO CARALPS, PEDRO GABARRO, ADOLFO LEY, JOSE ORIOL ANGUERA, AGUSTIN PEDRO PONS, JAIME PI FIGUERAS, JOSE M.ª POAL, ANTONIO PUIGVERT, RICARDO ROCA DE VIÑALS, JOSE M.ª SAMSO, RAMON SARRO, LUIS SAYE, RAMON SURINYACH and RAMON VIDAL-TEIXIDOR. 239 pages; 25 × 17 cm. (paper-bound). 1955. Instituto de Estudios Norteamericanos, Barcelona.

Practitioners' Conferences, Held at The New York Hospital-Cornell Medical Center. Volume I. Edited by CLAUDE E. FORKNER, M.D., F.A.C.P., Professor of Clinical Medicine, Cornell University Medical College, etc. 411 pages; 22 × 14.5 cm. 1955. Appleton-Century-Crofts, Inc., New York. Price, $6.75.

A Primer of Electrocardiography. 3rd Ed. By GEORGE E. BURCH, M.D., F.A.C.P., Henderson Professor of Medicine, Tulane University School of Medicine, etc., and TRAVIS WINSOR, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Southern California Medical School, etc. 286 pages; 24 × 15.5 cm. 1955. Lea & Febiger, Philadelphia. Price, $5.00.

Proceedings of the Third Medical Conference of Muscular Dystrophy Associations of America, Inc., New York, N. Y., October 8 and 9, 1954. (All of the material in this publication originally appeared in the *American Journal of Physical Medicine*, Volume 35, No. 1, February, 1955.) 324 pages; 25.5 × 17 cm. (paper-bound). 1955. Muscular Dystrophy Associations of America, Inc., New York.

Psychiatry for the Family Physician. By C. KNIGHT ALDRICH, M.D., Associate Professor of Psychiatry, University of Minnesota Medical School. 276 pages; 23.5 × 15.5 cm. 1955. The Blakiston Division, McGraw-Hill Book Company, Inc., New York. Price, $5.75.

Sexual Hygiene and Pathology: A Manual for the Physician. By JOHN F. OLIVEN, M.D., Psychiatrist to Vanderbilt Clinic, Columbia-Presbyterian Medical Center, New York, etc. 481 pages; 23.5 × 15.5 cm. 1955. J. B. Lippincott Company, Philadelphia. Price, $10.00.

The Spine: A Radiological Text and Atlas. By BERNARD S. EPSTEIN, M.D., Chief, Department of Radiology, The Long Island Jewish Hospital, New Hyde Park, New York. 539 pages; 26.5 × 18 cm. 1955. Lea & Febiger, Philadelphia. Price, $16.50.

Symposium on Atherosclerosis, Held Under the Auspices of The Division of Medical Sciences, National Academy of Sciences—National Research Council, at the Request of The Human Factors Division, Air Force Directorate of Research and Development, 22–23 March 1954. Publication 338, National Academy of Sciences—National Research Council. 249 pages; 25.5 × 17.5 cm. 1954. National Academy of Sciences—Research Council, Washington, D. C. Price, $2.00.

Viral Hepatitis: Clinical, Laboratory, and Public Health Aspects. By HEINZ F. EICHENWALD, M.D., Chief, Hepatitis Investigations Unit, Epidemiology Branch, Communicable Disease Center. 59 pages; 23.5 × 15 cm. (paper-bound). 1955. U. S. Department of Health, Education and Welfare, Public Health Service, Bureau of State Services. Available from Superintendent of Documents, U. S. Government Printing Office, Washington. Price, 55¢.